

Studies Towards the Total Synthesis of Patellazole B

This dissertation is submitted for the degree of Doctor of Philosophy

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August 2017

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit of 60 000 words.

Andrew Phillips

Cambridge, August 2017

Acknowledgements

The contents of this thesis would not have been possible without the hard work and support of numerous other colleagues, collaborators and support staff.

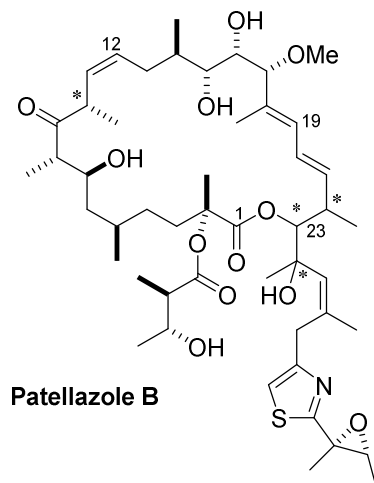
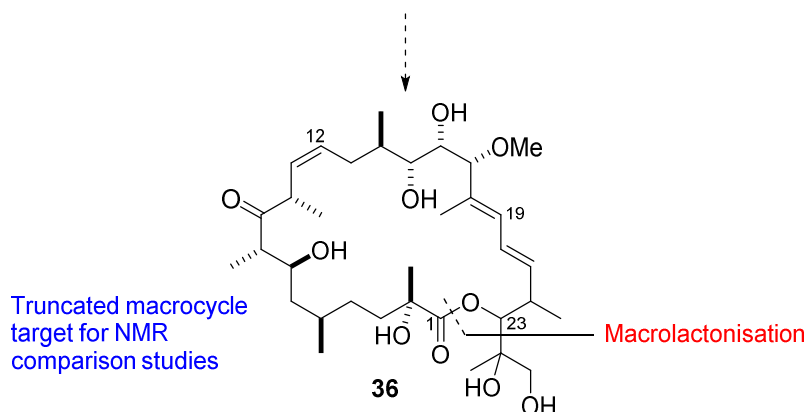
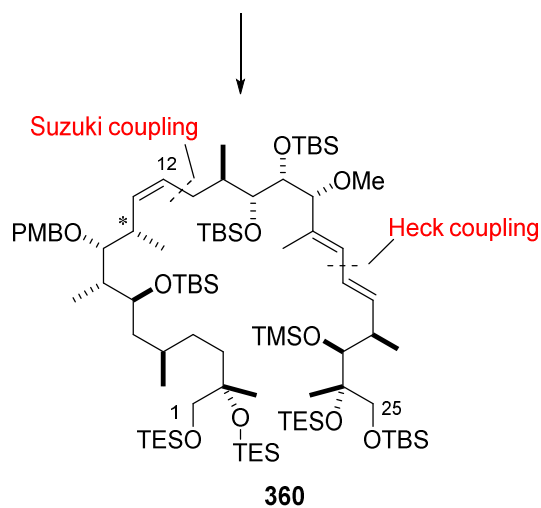
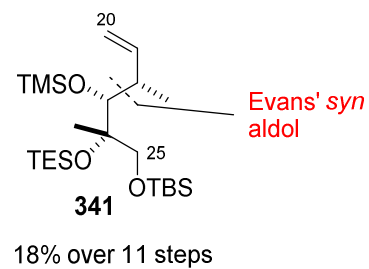
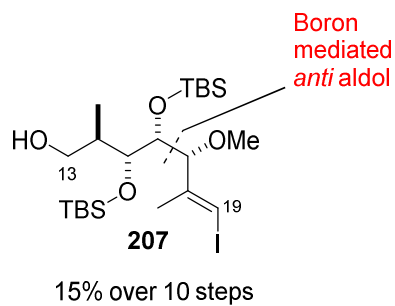
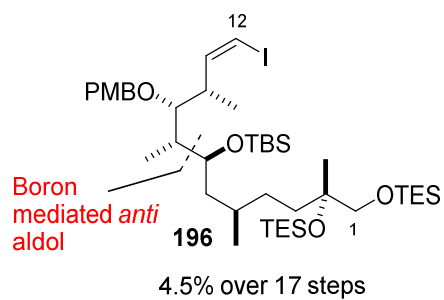
First and foremost, I would like to thank Prof. Ian Paterson for welcoming me into the group and providing me with funding, guidance and the opportunity to work on such a challenging and stimulating project.

I would also like to extend my gratitude to the three excellent Part III students, Bing Yuan Han, Tudor Balan and Matthew Anketell, who have joined me on this synthetic journey towards patellazole B and each contributed greatly towards their respective fragments.

I am extremely grateful to Dr Simon Williams for his support over the past four years. From setting the groundwork for this project at the start, to diligently proofreading this document at the end, with more useful discussions in between than I care to remember. My thanks also go to Adam Yip and Rachel Porter for their meticulous proofreading of the experimental section of this document and to Jolene Reid for help with computational modelling.

The work of any PhD would not be possible without a wide array of support staff. The excellent first floor technicians, Matt Pond, Nic Davies and Naomi Hobbs and the very knowledgeable NMR technicians, Dr Peter Grice and Duncan Howe deserve particular mention.

Finally, I would like to pay tribute to all the other members of the Paterson group that I have been fortunate to overlap with. I am particularly grateful for the running of NMR spectra, the generous lending of reagents and sharing of chemical expertise, but above all, creating the excellent working environment that is lab 122.



Summary

The patellazoles are a family of marine polyketide natural products first isolated from *Lissoclinum patella* in 1988 by both the Moore and Ireland groups. They exhibit significant cytotoxicity against the HCT 116 human colon tumour cells. To date however, their full 3D stereostructure have yet to be elucidated, which has hindered their development as potential drugs, and hampered full investigation into their biological mechanism of action and has deterred total synthesis efforts. This thesis describes synthetic efforts towards Patellazole B, which exhibits the highest potency of the three main congeners. To fully elucidate the structure and renew interest in the patellazoles as anticancer compounds, we have developed a flexible and modular synthesis that aims to define the unknown stereocentres within the pertinent region and allow for rapid fragment union. Compound **36** has been chosen as an initial target for NMR comparison studies. The synthesis of all eight diastereomers of this macrocycle should aid determination of the four unknown stereocentres.

Chapter 2 describes the synthesis of the C₁–C₁₂ fragment, focusing on the configuring of the C₅ methyl stereocentre and the construction of the C₇–C₁₀ stereotetrad *via* a boron-mediated *anti* aldol with an *in-situ* reduction. In the third chapter, the synthesis of the C₁₃–C₁₉ fragment is outlined. A boron-mediated glycolate aldol has been used to install the C₁₆–C₁₇ *anti* stereochemistry and a substrate-controlled reduction at C₁₅ delivered the hydroxyl with high diastereoselectivity. Studies into the C₁₇ methylation are also described.

Chapter 4 describes the synthesis of one possible diastereomer of the C₂₀–C₂₅ fragment, as a template for the preparation of the other 7 possible diastereomers. The route therefore employs only catalyst based control methods to install the three stereocentres, utilising a Sharpless asymmetric epoxidation and Evans aldol to construct the stereotriad. The 22*R*, 23*S*, 24*S* diastereomer has been initially chosen to investigate the later chemistry.

Chapter 5 contains discussion of the ongoing work investigating fragment union and formation of the macrocycle. A Heck coupling reaction has been employed to construct the C₁₉–C₂₀ bond and a Suzuki coupling reaction has been developed to facilitate the C₁₂–C₁₃ bond formation. These two cross couplings have delivered the C₁–C₂₅ fragment, **360**, the final compound reported in this thesis, which is three steps away from the completed macrocycle and six from compound **36**.

The experimental procedures and spectroscopic characterisation of the synthesised intermediates can be found in Chapter 6 and the Appendix.

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Abbreviations

4Å MS	4 Ångstrom molecular sieves
Ac	Acyl
acac	Acetylacetone
<i>aq</i>	Aqueous
Ar	Unspecified aromatic group
AT	Acyl transferase
BAIB	<i>Bis</i> -acetoxyiodobenzene
BBN	Borabicyclo(3.3.1)nonane
bp	Boiling point
BINAP	2,2'- <i>bis</i> (Diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1', Bi-2-naphthol
Bn	Benzyl
Bz	Benzoyl
<i>c</i>	Concentration
calc.	Calculated
CAN	Cerium ammonium nitrate
CHP	Cumene hydroperoxide
COSY	¹ H - ¹ H Correlation spectroscopy
CuTC	Copper(I)-thiophene-2-carboxylate
Cy	Cyclohexyl
δ	Chemical shift
DBB	4,4'-Di- <i>tert</i> -butylbiphenyl
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarisation transfer
DET	Diethyl tartrate
DFT	Density functional theory
DIPT	Di- <i>iso</i> -propyl tartrate
(DHQ) ₂ AQN	Hydroquinine anthraquinone-1,4-diyl diether
(DHQ) ₂ PHAL	Hydroquinine 1,4-phthalazinediyl diether

(DHQH) ₂ PYR	Hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether
(DHQD) ₂ PHAL	Hydroquinidine 1,4-phthalazinediyl diether
DFT	Density functional theory
DIBAL	Di- <i>iso</i> -butyl aluminium hydride
DIPA	Di- <i>iso</i> -propylamine
DIPEA	Di- <i>iso</i> -propylethylamine
DQCOSY	Double quantum correlation spectroscopy
DMAP	4-(<i>N,N</i>)-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	<i>N,N'</i> -Dimethyl- <i>N,N'</i> -propylene urea
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dppf	1,1'- <i>bis</i> (Diphenylphosphino)ferrocene
dr	Diastereomeric ratio
ee	Enantiomeric excess
equiv.	Equivalent(s)
Et	Ethyl
FT-IR	Fourier transform infra-red spectroscopy
h	hour(s)
HCT	Human colon tumour
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HRMS	High resolution mass spectrometry
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum coherence spectroscopy
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IC ₅₀	Half-maximal inhibitory concentration
imid.	imidazole
INADEQUATE	Incredible natural-abundance double-quantum transfer experiment
INEPT	Insensitive nuclei enhanced by polarization transfer

IPA	<i>iso</i> -propyl alcohol
IR	Infra-red
<i>J</i>	Coupling constant
L	Ligand
LDA	Lithium di- <i>iso</i> -propylamide
lut.	lutidine
mCPBA	<i>meta</i> -Chloroperbenzoic acid
M	Molar
Me	Methyl
min	minute(s)
Ms	Mesyl
MsO	Methanesulfonate
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
nM	Nanomolar
NBS	N-Bromosuccinamide
NIS	N-Iodosuccinamide
NMO	4-Methylmorpholine- <i>N</i> -oxide
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Överhauser effect
NOESY	Nuclear Överhauser effect spectroscopy
OTf	Trifluoromethanesulfonate
P	Unspecified protecting group
PE	Petroleum ether, bp 40-60 °C
PE ₃₀₋₄₀	Petroleum ether, bp 30-40 °C
Ph	Phenyl
pM	Picomolar
PMB	<i>para</i> -Methoxybenzyl
PMBTCA	<i>para</i> -Methoxybenzyl trichloroacetimidate
PMP	<i>para</i> -Methoxyphenyl
ppm	Part(s) per million
PPTS	Pyridinium <i>para</i> -toluenesulfonate

<i>quant.</i>	Quantitative yield
R	Unspecified substituent
R _f	Retention factor
RNA	Ribonucleic acid
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
R _t	Retention time
rt	Room temperature
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
SCUBA	Self-contained underwater breathing apparatus
<i>t</i> -	<i>tertiary</i> -
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBHP	<i>tert</i> -Butyl hydroperoxide
TBME	<i>tert</i> -Butyl methyl ether
TBS	<i>tert</i> -Butyldimethylsilyl
TCBC	Trichlorobenzoyl chloride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)-oxyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TfO	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tol	Tolyl
TOCSY	Total correlation spectroscopy
Ts	Tosyl
UV	Ultraviolet
ν _{max}	Infra-red absorption maximum
wt.	Weight

Nomenclature

Compound Numbering

Numbering priorities according to the IUPAC numbering system are used for the naming of compounds in the experimental section. However, for compounds relating to patellazole B and its fragments, the numbering used is that proposed by Moore, with the exception of the methyl groups, which are denoted by the skeletal carbon to which they are appended (**Figure 1**).¹ This numbering system is given on structures and also used in ¹H NMR assignments. For compounds not related to patellazole B, atom numbers are denoted by a prime.

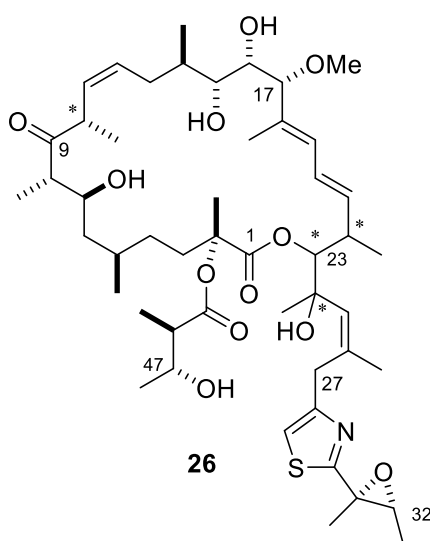


Figure 1: Numbering convention for patellazole B

Syn and Anti Isomers

The *syn* and *anti* convention for assigning the relative stereochemistry of adjacent stereocentres is used. Considering the carbon backbone of the compound to lie in a plane, a *syn* product is defined as having both vicinal substituents (R_3 and R_4) on the same side of the plane. Conversely, an *anti* product will have these substituents on opposite sides of the plane (**Figure 2**). This follows the convention for aldol adducts described by Masamune.²

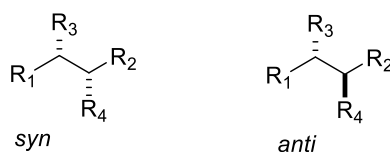


Figure 2: Examples of stereochemical relationships

Chapter 1: Introduction

1.1 Marine Natural Products as Therapeutic Agents

Throughout history, compounds found in nature have been used in traditional medicines.^{3,4} Although natural products from marine sources have been used less in traditional medicine than those from terrestrial sources, primarily for reasons of accessibility, the size and varied nature of the oceans lead them to hold great potential as a source of chemotherapeutic agents.^{5,6} Notably 32 of the 33 animal phyla have some representation in aquatic environments meaning that the oceans represent one of the most ecologically diverse environments on the planet.⁷ The unique environment of the oceans also often causes marine natural products to belong to unique chemotypes not found in terrestrial sources.^{8,9} The need to combat environmental and predatorial pressures has led even the simplest of marine bio-organisms to evolve the production of secondary metabolites as a means to survive. Whilst these metabolites are not essential to life, they provide an evolutionary advantage in self-defence or attracting prey. Despite being evolved for a specific target, these compounds frequently display interesting biological activity against a wide range of other targets, providing a useful source of inspiration and lead structures for the drug discovery industry.¹⁰ Natural products also typically display greater bioavailability (and structural diversity) than compounds developed from a combinatorial library, due to their evolution within nature.¹¹

Studies show that 50% of all new drugs released between 1981 and 2014 can be categorised as being ‘naturally inspired’ and for the 155 chemical-based anti-cancer drugs available in the West and Japan between 1940 and 2006, this rises to 73% (113 in total).¹² These include natural products, those derived from a natural product (typically having undergone a semisynthetic modification) and drugs made by total synthesis, but where the pharmacophore was from a natural product.⁵

Technological advances in the second half of the 20th century, such as the use of self-contained underwater breathing apparatus (SCUBA) diving equipment have made marine natural products far more accessible to the isolation chemist.^{11,13} Prior to 2004 only two marine natural product inspired drugs, cytarabine and vidarabine had been approved for market (in 1969 and 1976 respectively). Since the turn of the century though, a series marine natural product derived drugs have been released, including trabectedin¹⁴ and ziconotide¹⁵ and as of 2010 a further 11 compounds were in the clinical pipeline.¹⁶

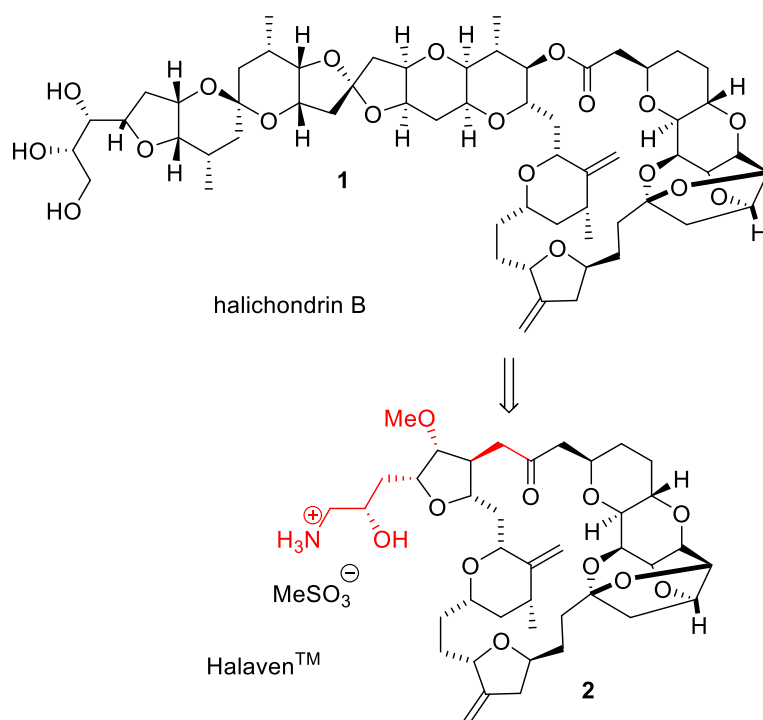


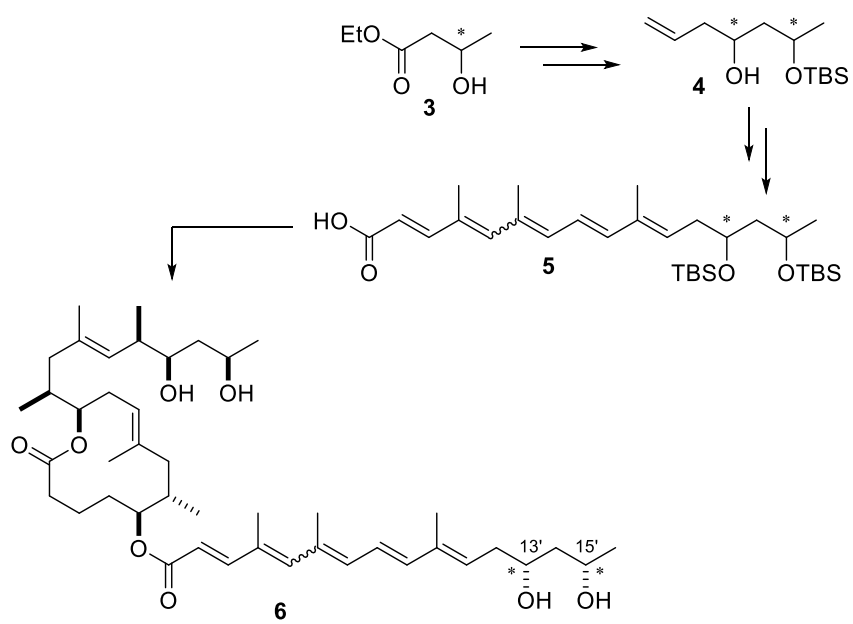
Figure 3: Structural deletion of halichondrin B to give Halaven™ (Eribulin mesylate)

A perpetual issue with natural products as drug candidates however, is their scarce natural abundance. Typical isolation yields are extremely low and thus the extraction of clinically useful quantities requires the collection and slaughter of multi-tonne quantities of the organism. Artificial attempts to produce greater quantities of the bioactive material through farming of the marine organism often fail due to the significant effect of environmental influences on the production of secondary metabolites. For these reasons, organic synthesis still represents one of the only realistic options to produce these compounds, in the quantities required for clinical evaluation. Moreover, fragment or total synthesis provides the opportunity for the unambiguous confirmation of the structural configuration and also the development of new synthetic methods. Furthermore, a synthetic investigation may also provide insight into the likely biosynthesis.¹⁷

Polyketides represent one such class of natural products and have been isolated from a variety of different marine invertebrates, such as corals, sponges, algae and other microorganisms.¹⁸ These compounds have complex molecular architectures, with high levels of oxygenation, dense arrays of stereocentres and exhibit potent biological activities. A large number of these compounds have now succumbed to total synthesis, due to their interest to synthetic chemists as potential drug targets.³ Recent developments in the field have led to more concise routes, allowing the synthesis of increasingly complex targets.^{8,19–21} Despite this, the total synthesis of complex polyketide natural products still represents a significant, yet rewarding challenge for the synthetic chemist.

Total synthesis also usefully provides the possibility of producing structurally related analogues, allowing for structure-activity relationship studies to be undertaken, with a view to further understanding the mode of action of the compound. These modifications could also be used to make the molecule more 'drug-like', with improved pharmacokinetics and reduced toxicity. Danishefsky has described the art of 'Diverted Total Synthesis'; reducing the complexity in natural products, simplifying their syntheses and making them more amenable to the pharmaceutical industry.²²

A compelling example of this theory in practice is that of the marine natural product halichondrin B from which the anticancer drug eribulin mesylate (Halaven®) is inspired (**Figure 3**).²³ The natural product underwent significant structural deletion, particularly of the side chain, which was found not to have any effect on the compound's cytotoxicity. A functional group modification from the macrolactone to a cyclic ketone was also discovered to improve the *in vivo* stability.²⁴ The final manufacturing route is still more than 30 steps in the longest linear sequence, representing a major industrial undertaking and proof that total synthesis can provide a viable and realistic supply route to even the most complex



Scheme 1: Complete structure of mycolactone C, as determined by total synthesis

molecules. Moreover, this work was only made possible by the total synthesis of the full natural product, halichondrin B by Kishi.²⁵ X-ray crystallography had unambiguously assigned the full stereostructure of norhalichondrine A, but this wasn't possible for halichondrin B. Comparison of spectral data between the synthetic material and the both natural products allowed unambiguous assignment of the absolute and relative stereochemistry within halichondrin B for the first time.

In summary, the fields of natural product chemistry and organic synthesis increasingly complement one another. Natural products provide great inspiration for the drug discovery chemist and in attempting to realise their potential and produce these highly complex compounds, the synthetic chemist is encouraged to develop new methodology and advance the field of organic chemistry.

1.2 Use of Total Synthesis as a Means of Structural Determination

Improvements in purification and analytical techniques, such as high performance liquid chromatography (HPLC) and high field NMR spectroscopy have made full structural determination possible on sub-milligram quantities of material.²⁶ Despite these developments though, more than 300 structural revisions to natural products have been made since 1990.²⁷ Synthetic efforts have been critical in almost all these revisions and ultimately total synthesis has proved to be a powerful tool in providing categorical validation of the true chemical structure. A key aspect of total synthesis therefore is its ability to determine, confirm or correct the true structure of a natural product.

Kishi's synthesis of mycolactone C is a useful example of using a total synthesis as a means of structural determination (**Scheme 1**).²⁸ Whilst he could determine the stereochemistry of the macrocycle and northern side chain *via* a process of fragment synthesis and NMR comparison to the natural product in that region, this proved impossible in the southern side chain. The natural product exists as a 1:1 mixture of *E/Z* geometric isomers across the C_{4'}-C_{5'} bond, complicating spectroscopic analyses, particularly of the polyunsaturated side chain. The remote nature of the C_{13'}-C_{15'} diol, away from the macrocyclic core also provided a challenge as to how to predict the relative stereochemistry between these two regions with confidence. Limited natural product availability also perturbed degradation studies. Synthesis of all four stereoisomers followed by a combination of NMR and HPLC analysis was used to determine the stereochemistry of the natural product.

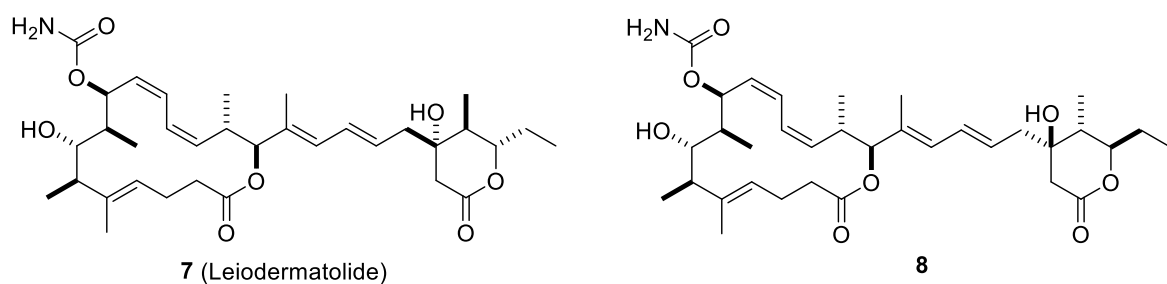


Figure 4: The structures of leiodermatolide (7) and its lactone anitpode (8)

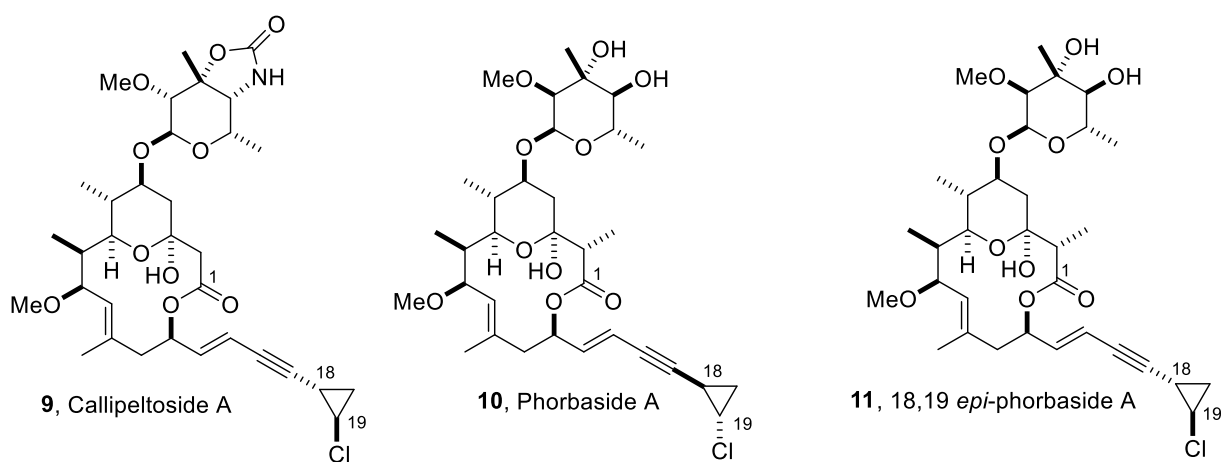


Figure 5: Chemical structures of callipeltoside A, phorbaside A and its (18S, 19R) diastereomer

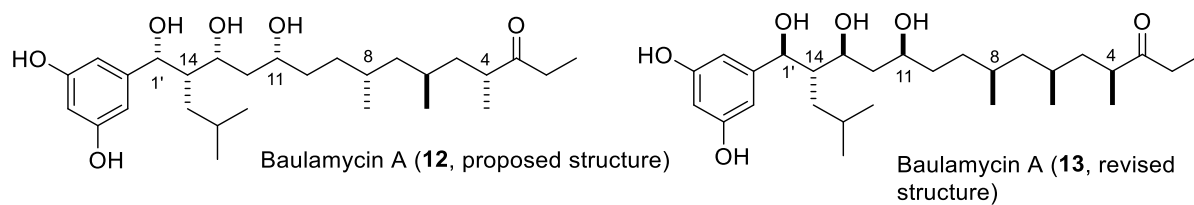


Figure 6: Proposed and revised structures of baulamycin A

The full stereostructure of leiodermatolide could also not be assigned from the isolated sample. Despite the use of advanced NMR techniques, combined with molecular modelling and computational NMR prediction, only the relative configurations of the macrolide core and the δ -lactone could be determined. The pentadienyl spacer unit between these two regions made correlating these two stereoclusters impossible. Through synthesis and attachment of both antipodes of the δ -lactone to the macrocycle, Furstner could identify the true structure.^{29,30} Comparison of **A** and **B** (**Figure 4**), by NMR indicated the former as leiodermatolide. Only very subtle spectroscopic differences between **A** and **B** were observed, highlighting the critical role of total synthesis in the structural determination.

The Paterson synthesis of phorbaside A also provided configurational validation.³¹ Spectroscopic analysis of phorbaside A showed significant structural similarity to callipeltoside A.^{32–34} Semiquantitative circular dichroism using model fragments however, indicated the configuration of the cyclopropane ring (18*R*, 19*S*) in phorbaside A to be opposite to that of the callipeltosides (**Figure 5**). Paterson proceeded to synthesise both the proposed structure (**10**) and its (18*S*, 19*R*) diastereomer (**11**). Whilst ¹H and ¹³C NMR spectra of both samples were identical to the natural product, they were distinguishable by circular dichroism, validating the proposed structure, with an antipodal cyclopropane configuration to the callipeltosides.

Initial synthetic attempts by both Aggarwal³⁵ and Goswami³⁶ towards total synthesis of baulamycin A found that the spectroscopic data for the synthetic material did not match that of the natural material, indicating a misassignment of the stereochemistry (**Figure 6**). The inherent flexibility of the carbon chain, along which there are seven stereogenic centres, leads to multiple conformations of the molecule being present in solution. The weighted average of these displayed in the natural NMR spectrum, severely complicates the configurational analysis. With synthesis of all 128 possible stereoisomers an implausible solution, extensive NMR analysis of individual fragments alongside computational modelling was carried out by Aggarwal. ROESY data from the natural sample aided deduction of the relative stereochemistry in the C₁₁-C₁₄ region. With the stereocentres in the C₄-C₈ region non-contiguous however, such an approach was not possible. Assembly-line synthesis³⁷ was used to produce a mixture of four stereoisomers of the baulamycins, with the newly assigned stereochemistry in the C₁₁-C₁₄ region, but differing configurations at C₄, C₆ and C₈. These stereoisomers were produced in an unequal (but predetermined) mixture by variation of the reagent stoichiometry in the assembly line synthesis. Analysis of the signal intensities in the ¹³C spectrum of the mixture was used to determine which stereoisomer in the mixture most closely replicated the natural sample. This method established the relative stereochemistry of the C₁₀-C₁ fragment and synthesis of the C₁₁/C₈ *syn* and C₁₁/C₈ *anti*

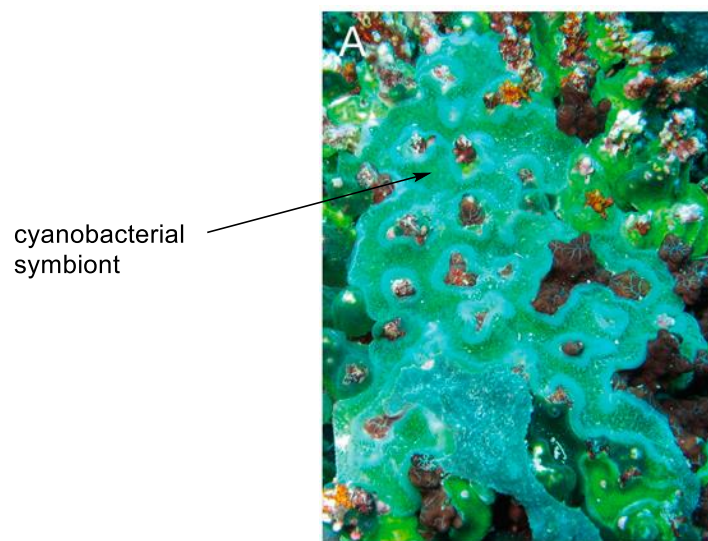


Figure 7: Photograph of *L. patella* sample L3 at collection site in the Solomon Islands⁴⁹

diastereomers was used to determine which diastereomer was the natural one. Optical rotation then aided identification of the correct enantiomer.

All these examples illustrate the power of total synthesis in structural determination. Despite the advances in NMR spectroscopy and computational prediction, often it is only the synergy of these tools alongside synthetic efforts that is able to provide elucidation or validation of a correct natural product structure.

1.3 The Patellazoles

1.3.1 Isolation Attempts

The patellazoles are a family of marine natural products isolated from *Lissoclinum Patella*, a didemnid tunicate found in various locations of the Pacific Ocean.³⁸ Didemnid tunicates are a type of marine chordate recognised for their symbiotic relationship with unicellular algae.^{39,40} It has been reported that algae of the genus *Prochloron* are the only known symbionts of *L. Patella*,⁴¹ but this was not further investigated at the time of patellazole isolation. This cyanobacterial symbiont can be seen as a dark green mottling below the surface of the tunicate (**Figure 7**).³⁸

In 1988 the Ireland⁴² and Moore¹ groups simultaneously reported that *L. Patella*, collected from the Fiji and Guam respectively, contained a family of thiazole-containing polyketide metabolites, which they named the patellazoles. The original interest in the tunicate was prompted by the apparent geographical dependency on the secondary metabolite composition and abundance.³⁸ Evaluation of *L. Patella* extracts from the Philippines, Australia and Indonesia for instance, had failed to yield any of the patellazoles. Other biologically active compounds isolated from *L. Patella* extracts include patellins 1-6 and Ulithiacyclamide B.^{43,44} *Prochloron didemni* has also been shown to produce a series of cyclic peptides; the patellamides, which are far more ubiquitous amongst *L. Patella* samples.⁴⁵

Crude lipophilic extracts (extracted using hexanes, carbon tetrachloride and chloroform) showed promising cytotoxic potency (IC₅₀ 15 ng / mL) against the KB human cancer cell line, which is a contaminated human oral epidermoid carcinoma cell line.^{46,47} Purification of the crude extracts by silica gel chromatography and reverse phase HPLC yielded three congeners of the patellazole family, namely patellazoles A - C. Both groups published proposed 2D structures, with Zabrinke and Ireland describing the structural elucidation of patellazole C and Corley, Moore and Paul that of patellazole B. Isolation

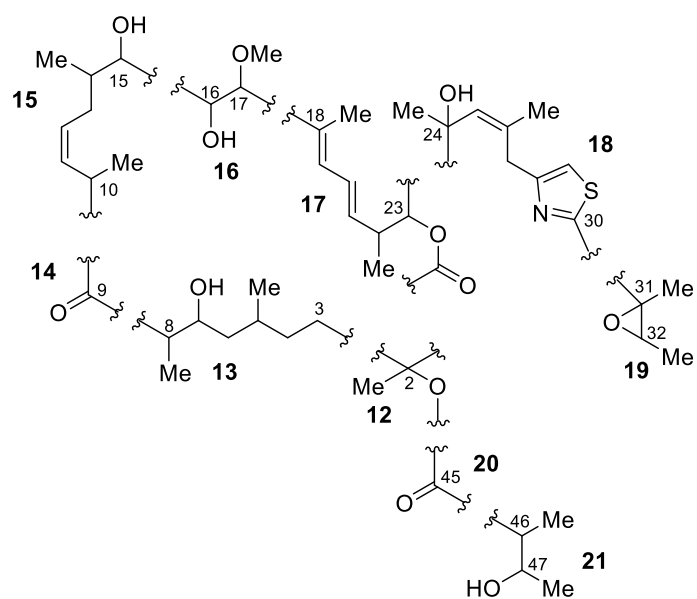


Figure 8: Sub-units A-J identified in 2D structural determination by Moore

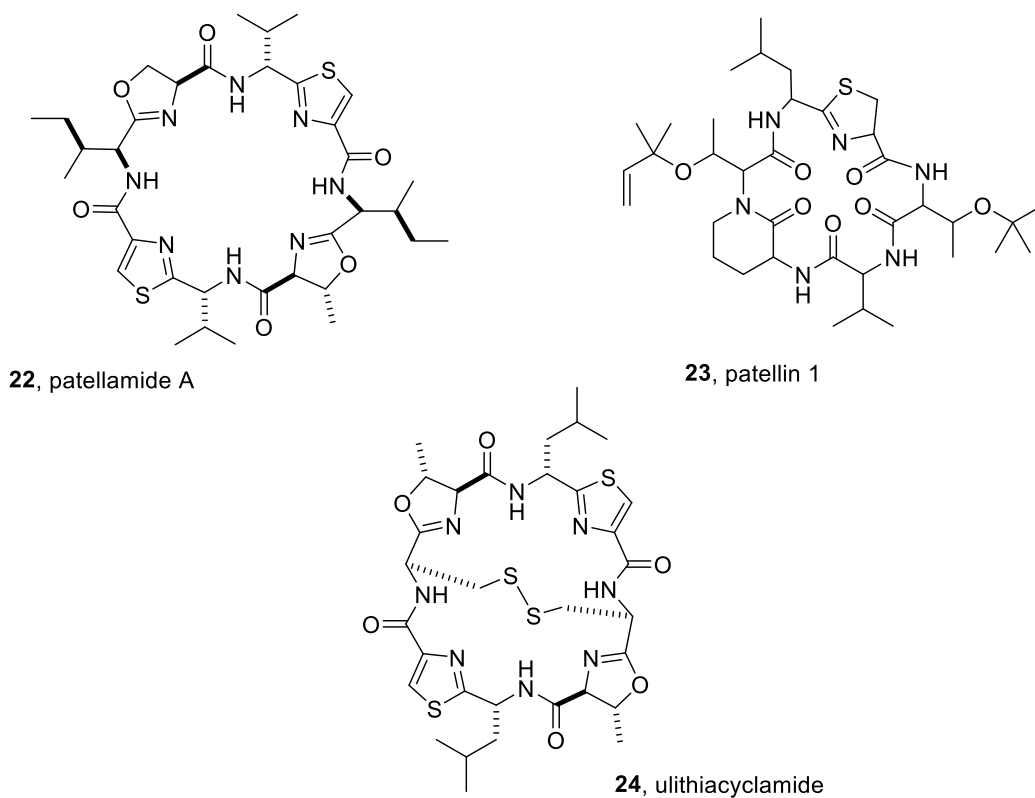


Figure 9: Other bioactive natural products isolated from *L. patella*

yields by Ireland were as follows: 96.5 mg of patellazole A, 144.3 mg of patellazole B and 312 mg of patellazole C from 220 g of freeze-dried organism. These are notably high, compared with typical natural product isolation yields. Paul reported the isolation of 12 mg of patellazole B (0.75% from crude extracts).

The 2D structural elucidation of patellazole B was carried out by Moore utilising numerous characterisation techniques.¹ IR data indicated the presence of both a ketone and an ester as well as several hydroxyl groups. High resolution electron ionisation mass spectrometry (EIMS) established a molecular formula of $C_{49}H_{77}NSO_{12}$. Further analysis by ^{13}C and 1H NMR identified one ketone carbonyl, two ester carbonyls and a thiazole system. An attempt to desulfurise patellazole A was made by Zabriskie.³⁸ Treatment with excess Raney nickel instead proceeded to confirm the presence of an epoxide (through its subsequent reduction). The observed resistance to desulfurisation with Raney nickel did however rule out the existence of a thiol, thioether or thioamide. Ozonolysis of patellazole C proceeded to deliver a single UV active product, with high field ^{13}C NMR signals closely matching those of 2-*t*-Bu-4-methylthiazole, serving to confirm the presence of a thiazole moiety in the patellazole family.

72 protons were identifiable from investigation of the DEPT edited ^{13}C NMR data, indicating the presence of five hydroxyl moieties. A series of 2D 1H NMR techniques (COSY, TOCSY, phase-sensitive NOESY and ROESY) were used to identify ten partial sub-units (as shown in **Figure 8**), which could then be connected into a complete 2D structure using 1H - ^{13}C correlation experiments (HMBC and HSQC). NOE analysis was used to establish the *E* and *Z* geometries of the C_{18} - C_{19} and C_{25} - C_{26} alkenes respectively, as well as the *cis* geometry of the epoxide and the location of the C_{17} methoxy group. Vicinal coupling constant analysis was used to determine the *E* and *Z* geometries of the remaining macrocycle olefins in patellazole B. Ireland used other 1D and 2D NMR experiments, including selective INEPT, phase-sensitive INADEQUATE and DQCOSY to elucidate the structure of patellazole C.

The three major patellazole congeners share many of the same features; a 24-membered macrolide ring, with a side chain containing a thiazole and an epoxide, and 15 or 16 stereocentres. These congeners differ only by oxygenation at the C_{10} methyl group and C_{34} positions (**Figure 10**). Interestingly, a common feature across almost all the natural products extracted from *L. patella*, including the patellins, the patellamides and ulithiacyclamide is the presence of a thiazole or thiazoline (**Figure 9**).

In addition to the three major congeners (A-C), a further four minor secondary metabolites were isolated, although their structures were not fully assigned, due, in part, to the very low isolation yields. Patellazoles D and E (2.5 mg combined, in a 5:3 ratio) were extracted as an inseparable mixture. With parent ions at m/z 938 and m/z 906 they were postulated to be an additionally hydroxylated isomer of patellazole C and a dihydropatellazole B. Patellazole F (6.8 mg) was hypothesised to be the C_7 epimer of Patellazole C, based on the similarity in elution times and only minor differences in ^{13}C shifts. Patellazole G (3.5 mg) was solely isolated from the hexane fraction during the extraction of the crude material. The 12 olefinic signals in the ^{13}C NMR, alongside a parent ion at m/z 872 indicated that patellazole G might be 31,32-deoxypatellazole A. Initial NMR comparison was promising, with the 1H NMR spectrum superimposable with the semi-synthetic compound produced by treatment of the corresponding natural product with Raney nickel as described previously. Sample degradation prohibited full assignment however.

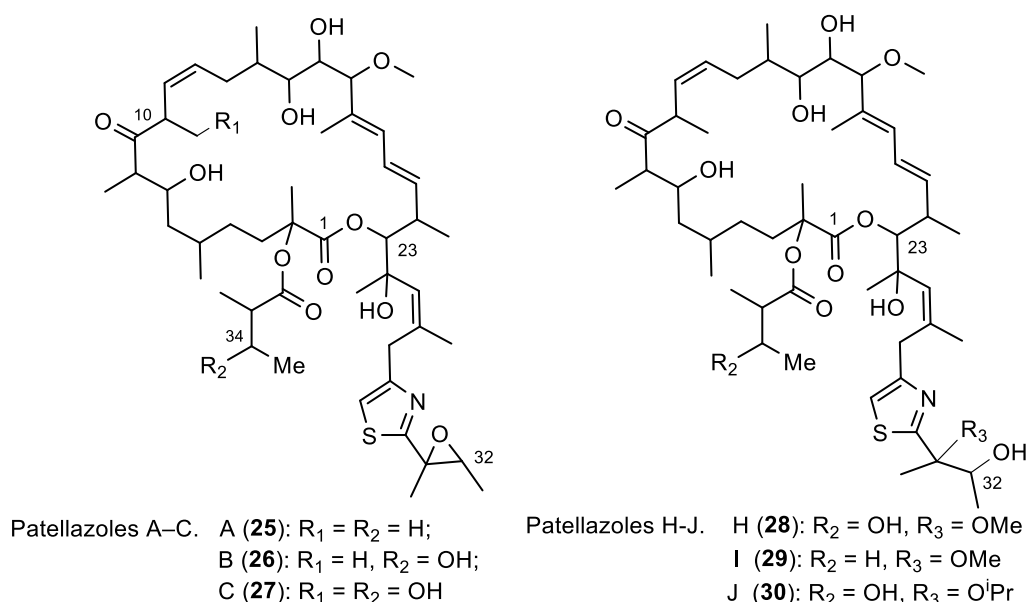


Figure 10: Congeners of the patellazole family

Recollection of *L. patella* in January and August of 2001 from the same site as in 1984, 1987 and 1997 (the Astrolabe Reef, Kandavu) aimed to provide enough samples of the patellazoles for further biological testing. These extracts however, failed to yield any of the patellazoles. A further effort, by the Ireland group, to re-isolate these compounds from samples of *L. patella* collected around the Navula pass in Fiji in July and September 2001 however, did produce patellazoles in similar yield to previous collections. This would suggest the occurrence of localised incidents resulting in patellazole biosynthesis being turned on or off in *L. patella*, rather than a seasonal environmental factor such as temperature or nutrient availability.

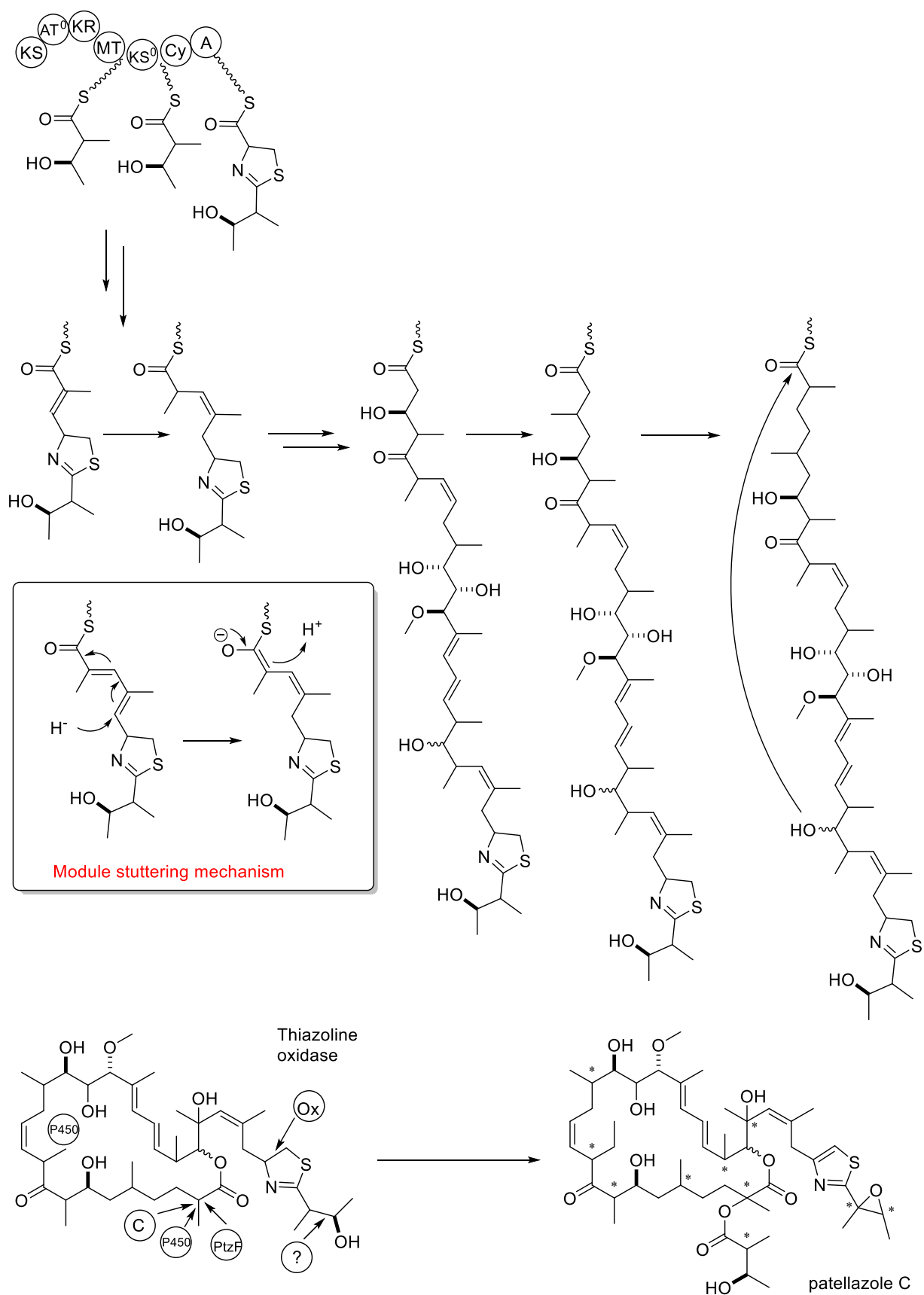


Figure 11: Proposed biosynthetic pathway by Schmidt

However this re-extraction proved far from trivial and also resulted in the isolation of several new analogues, patellazoles H-J (**Figure 10**).⁴⁸ These differ from patellazoles A-B only in the lack of an epoxide moiety and appear to exist as an artefact of the isolation procedures used, with the epoxide having undergone nucleophilic opening by the HPLC solvents used (MeOH and *i*-PrOH). Although originally postulated that the epoxide had been opened at C₃₂, further characterisation indicated that nucleophilic attack had instead taken place at the carbon alpha to the thiazole ring, with a developing positive charge best stabilised at this position. Isolation yields of these artefacts were low (1.7 mg, 0.7 mg and 0.6 mg of patellazole H, patellazole I and patellazole J respectively), but provided sufficient material for initial biological testing.

1.3.2 Stereochemical assignment

In 2012, Schmidt sought to investigate the likely biosynthetic pathway to the patellazoles.⁴⁹ Genetic analysis of *Prochloron didenmi* and the cloacal habitats failed to yield any polyketide synthase (PKS) genes, but DNA sequencing of the zooid region surrounding the cloacal cavity led to the discovery of *Candidatus* 'Endolissoclinum faulkneri', an α -proteobacterium; the likely producer of the patellazoles.^{45,49} A retrosynthetic analysis indicated the incorporation of 15 acetate units and a cyclised serine, plus the addition of a further two acetate units in the side chain. Schmidt has proposed a plausible biosynthetic pathway to the patellazoles (**Figure 11**) and using genetic analysis of the ketoreductase domains in the pathway, he has been able to predict the configuration of five out of the 16 stereocentres, specifically the oxygenated centres at C₇, C₁₅, C₁₇, C₃₁ and C₄₇.⁴⁹

An unusual feature within the patellazole biosynthesis is the presence of two β - γ *cis*-double bonds. These are rare in polyketide-synthase-produced natural products and the lack of a dehydratase domain within the relevant module, indicates a novel pathway may be involved in their biosynthesis. Schmidt has proposed the synthesis of a thioester-conjugated 1,3-diene, which subsequently undergoes a reductive mechanism. Action of a 2,4-dienoyl-CoA-reductase enzyme on the diene, generates a 1,2,3,4-dieneolate, which is then protonated to give the β - γ *cis*-alkene.

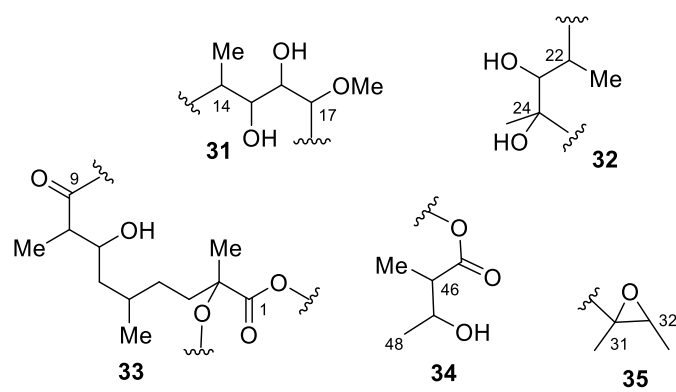


Figure 12: Key structural truncates identified by Yoshida for NMR studies

Various accessory proteins are required in the proposed biosynthetic pathway. Unlike most PKS proteins, which contain an acyl transferase (AT) domain in each module, the patellazole synthesis utilises ATs on a separate protein to deliver malonate units onto the acyl-carrier proteins to install most of the methyl groups along the backbone. Additional accessory proteins are responsible for the β -methylation at C₅. Several post-cyclisation processes are required, including a regio- and stereoselective P450 oxidation at C₂ and optionally at Me₁₀, attachment of the ester side chain and an as yet undetermined process to install the epoxide moiety.

Studies by Moore and Yoshida⁵⁰ in 2002 attempted to elucidate the stereochemical configuration of patellazole B, using various NMR techniques, including analysis of NOE and coupling constant data. Using the *J*-based configurational analysis method developed by Murata,⁵¹ Yoshida was able to determine the predominant conformer in solution for a series of C-C bonds along the backbone by combining the analysis of $^2J_{C-H}$, $^3J_{C-H}$ and $^3J_{H-H}$ data. Each set of data follows a Karplus style relationship,⁵² thus allowing *gauche* or *anti* relationships to be determined. When one of these stereogenic carbons is oxygenated, the relative configuration can also be determined. The electronegativity of the oxygen has a sufficient effect on the $^2J_{C-H}$ value between the oxygenated carbon and a proton on the adjacent carbon that the spatial relationship between the two can also be identified as *anti* or *gauche*. For each C-C bond, the two possible diastereomers will collectively have six rotamers. Through a process of elimination, the coupling constant information can be combined to ascertain the relative conformation and configuration of the two adjacent stereocentres. NOE analysis is still required though to distinguish between the two *anti*-diastereomers. Since the exploration of the biosynthetic pathway by Schmidt has proposed the stereochemistry at the majority of the oxygenated centres, these relative conformations could be reassigned as absolute configurations.

Yoshida fragmented patellazole B down into five key stereoclusters, namely C₁-C₉, C₁₄-C₁₇, C₂₂-C₂₄, C₃₁-C₃₂, and C₄₅-C₄₈ (**Figure 12**). NOE analysis was sufficient to determine the *cis*-relationship between the two methyl substituents on the epoxide at C₃₁ and C₃₂. For the other side chain (**34**), the adjacent stereocentres fitted well into a characteristic 1,2-methine system and an *anti*-relationship was determined between C₄₆ and C₄₇. For the C₁₄-C₁₇ stereotetrad, a *syn*-relationship between C₁₅ and C₁₆ was elucidated alongside C₁₄-C₁₅ and C₁₆-C₁₇ *anti* relationships. *Anti*-relationships were established between both C₅ and C₇ stereocentres and across the C₇-C₈ bond. Murata's method also aided the C₂ stereocentre to be determined as having an *S* configuration.

However, for the C₂₂-C₂₄ stereotriad, $^{2,3}J_{C,H}$ couplings were found to be of intermediate magnitude, possibly due to the molecule not adopting a staggered conformation in this region close to the macrocycle junction, or multiple conformers being present. For these regions, Murata's method is therefore not appropriate. NOE data was insufficient to determine the conformation unambiguously, so the full stereochemistry remains undetermined. Combining the studies by Schmidt and Yoshida, the configuration at 12 of the 16 stereocentres have been assigned with confidence (**Figure 13**).

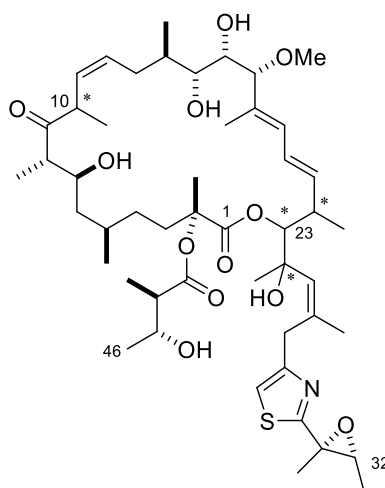


Figure 13: Currently assigned stereochemistry in patellazole B

Investigations carried out by Kenneth Ng in the Paterson group⁵³ aimed to help assign the configuration of the remaining unknown stereocentres by use of Goodman's DP4-based NMR prediction technique.⁵⁴ This technique uses a statistical method to compare the predicted chemical shift data for a compound to the experimental spectrum. Initially, a conformational search is undertaken and single point energy calculations carried out using DFT to deduce the lowest energy conformers for each candidate diastereomer. An NMR prediction for both the ^1H and ^{13}C chemical shifts is then carried out for each of these conformers and spectra combined to represent the calculated weighted average of these conformers. With predicted spectra produced for each candidate diastereomer, they can be compared with those spectra obtained from the natural product. A statistical model is then used to assign a confidence rating to each diastereomer based on the errors in the ^1H and ^{13}C shifts. Unfortunately, this work was unsuccessful in providing further insight into the unknown stereochemistry. It was postulated that the macrocycle is simply too flexible, causing there to be too many low energy conformers, for this methodology to offer sufficient confidence in a single diastereomer.

However, it was concluded that sufficient stereochemical information was in place to embark upon synthetic studies with the objective of assigning the remaining stereocentres through a total synthesis.

1.3.3 Biological evaluation

Besides the challenge of fully assigning the stereostructure of patellazole B, the interesting biological activity reported in the literature makes it a valuable target to pursue. The patellazoles were found to have significant cytotoxicity towards HCT 116 human colon tumour cells. A series of MTT assays, each of 72 hours and using DMSO as a vehicle were carried out to determine the cytotoxicity. This assay observes the activity of cellular mitochondria as a measure of total cell growth inhibition.⁵⁵ Actively respiring mitochondria produce succinate dehydrogenase, which converts the MTT (a soluble dye) into an insoluble crystal. Patellazoles A and B showed the greatest toxicity with both exhibiting low nanomolar IC₅₀ values across wild-type and p53 cell lines.⁵⁶ Patellazole B exhibited slightly higher potency in the wild-type case with an IC₅₀ value of 0.39 nM (**Table 1**). Patellazole C typically exhibited cytotoxicities an order of magnitude lower.

Patellazole congener	HCT 116 wild-type IC ₅₀ / nM	HCT 116 p53 ^{-/-} IC ₅₀ / nM	HCT 116 p21 ^{-/-} IC ₅₀ / nM
A	0.62	0.66	— ^a
B	0.39	0.62	— ^a
C	4.70	5.60	— ^a
H	30.0	34.0	9.0
I	8.80	8.30	2.4
J	2.60	3.00	1.0

^a Not tested

Table 1: Comparison of biological activity between patellazole congeners

The mode of action is still not fully understood, but it is known that all the different congeners show cytotoxicity *via* the same mechanism of action. Moreover, whilst the epoxide opening observed in patellazoles H-J does not completely abrogate their bioactivities, they exhibited cytotoxicities typically one to two orders of magnitude lower. This suggests that the relative cytotoxicity of the epoxide-opened patellazoles could be as a result of either an altered affinity with the target protein binding site or pharmacokinetic effects. These could lead to either a reduced ability of the compound to enter the cells or affect its distribution within the cell.

Studies by Ireland⁵⁷ have shown that the treatment of tumour cells with IC₅₀ concentrations of the patellazoles activates apoptotic pathways leading to cell death (**Table 2**). HCT 116 wild type cells were arrested at the G₀/G₁ and S phases of the cell cycle. After 24 hours, a greater percentage of cells were in the G₀/G₁ phase for all patellazole congeners compared with the control sample. After 48 hours, a decrease in the G₀/G₁ percentage was counterbalanced with a significant increase in the amount of cellular debris. So it is likely that cells which had arrested in the G₀/G₁ phase had either died or passed slowly to the S phase and re-arrested there.

Treatment	Duration (h)	G ₀ / G ₁ (%)	S (%)	G ₂ / M (%)	Debris (%)
Control	24	50.1	34.5	15.4	4.0
Patellazole A	24	60.6	29.0	10.4	5.0
Patellazole B	24	67.7	25.3	7.0	4.9
Patellazole C	24	71.2	19.3	9.6	6.7
Control	48	68.0	25.9	6.2	7.8
Patellazole A	48	60.5	32.1	7.4	16.0
Patellazole B	48	69.8	24.7	5.5	21.5
Patellazole C	48	62.3	31.2	6.4	17.5

Table 2: Cell cycle effect of IC₅₀ concentrations of patellazoles on HCT 116 wild-type cells

The third response observed was the effect on macromolecule synthesis. Radiolabelled precursors were injected into HCT 166 wild type cells which had been treated with a 30 nM solution of patellazole H. [³H] Thymidine, [³H] uracil and [³H] lysine were used to detect for DNA, RNA and protein production respectively. Comparison between the radioactivity of the treated cells and control samples then determined the level of macromolecule synthesis. An increase in DNA production upon treatment with patellazole H was initially observed, although this returned to control levels after 30 hours and it is unclear whether this would have continued to drop. Both RNA production and protein synthesis were shown to be decreased however. The inhibition of the latter appears to begin at around three hours and continues to decrease protein synthesis to only 13% of that of the control culture after 30 hours.

Lissoclinolide, another natural product isolated from *L. patella* had exhibited interesting cytotoxicity against three other cells lines; Caco2 (another colon tumour cell line) and two breast cancer lines (MDA-MB-435S and MDA-MB-468). Disappointingly, none of the patellazole congeners displayed promising biological activity against these lines.⁵⁷

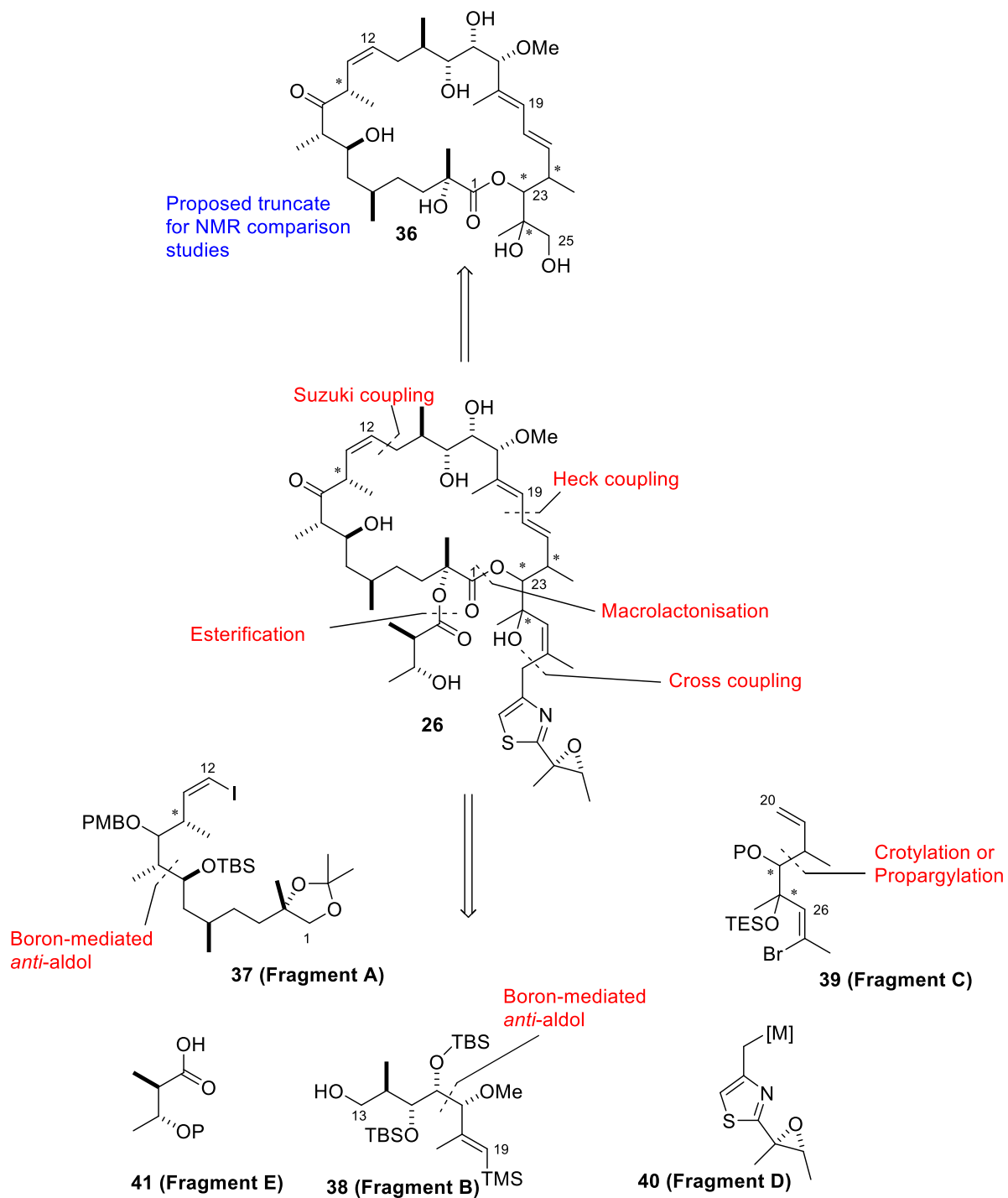
Several approaches are known to elucidate the cellular target of a cytotoxin, including high throughput screening, photoaffinity labelling and affinity chromatography. The latter of these was attempted by Richardson,⁴⁸ aiming to utilise a biotin-streptavidin linker to bind the patellazole to a solid phase support. Although the cytotoxicities of patellazole B and its epoxide-opened analogue patellazole H are different, it was considered that their bioactivities were similar enough to make use of this epoxide functional group as a linker junction. With no partial or total syntheses of the patellazoles to date, attachment of a linker selectively to a single hydroxyl group on the natural sample would have been challenging. Unfortunately, all attempts at linker addition by epoxide opening though proved fruitless. With greater quantities of the patellazoles available, ideally produced by total synthesis, far more extensive biological testing could be carried out. This might include further attempts at affinity chromatography or photo affinity labelling to determine the protein target and binding site. Synthesis of appropriate analogues would also allow structure-activity relationships to be determined.

1.4 Project Aims and Retrosynthetic Analysis.

To date there have been no attempted syntheses of any of the patellazoles disclosed, presumably because of continued uncertainty in the stereochemistry, where there are 65536 possible stereoisomers. However, as a result of the studies described in **section 1.3.2**, and only four of the 16 stereocentres remaining unassigned, it was felt that sufficient structural understanding of the patellazoles had been gained to embark upon a total synthesis. With biosynthetic, NMR and computational methods exhausted in pursuit of the complete 3D assignment, it was concluded that a key aspect of the project would be a complete structure determination by total synthesis.

A successful total synthesis should, in turn, allow for further biological testing to take place and structure-activity relationships to be investigated. With promising cytotoxic data obtained from natural sources, but an unknown mechanism of action,⁵⁷ this is an enticing prospect.

Patellazole B has numerous challenging structural features, which make it a motivating and thought-provoking target for the synthetic chemist. Alongside controlling the 16 stereocentres; the C₉ ketone, E,E-diene, unsequential *cis*-double bonds at C₁₁/C₁₂ and C₂₅/C₂₆ and the epoxide moiety all provide significant synthetic challenges.



Scheme 2: Retrosynthetic analysis for patellazole B

As outlined in **Scheme 2**, we envisaged that the molecule could be disassembled into five key fragments. Three of these (**37**, **38** and **39**) would form the macrocycle and the other two (**40** and **41**) the side chains. This modular approach of constructing highly functionalised fragments, with all the desired stereochemistry in place and at the correct oxidation level, should allow for efficient fragment coupling and a step-reduced endgame strategy.

With three of the four unknown stereocentres lying contiguously, we proposed to isolate them into a single fragment, which could be synthesised as the eight different stereoisomers and attached in turn to the rest of the macrocycle. We intended to ensure flexibility in the order of fragment coupling, although we envisaged that for the synthesis of multiple macrocycle stereoisomers, the attachment of any isomer of the C₂₀-C₂₆ fragment to a complete C₁-C₁₉ fragment would be the most convergent. Macrocycle formation could also either be carried out *via* a macrolactonisation or an intramolecular cross coupling reaction.

The C₁₀ methyl stereocentre has not been assigned, but we have decided to target the 10*S* configuration as the 1,4-*syn* boron aldol methodology developed in the Paterson group should provide an efficient approach to construct it.⁵⁸

Key disconnections could take place at the C₁ lactone, adjacent to the C_{11/12} alkene and across the C_{18/21} diene region, thus dividing the macrocycle into three key components, **37**, **38** and **39**. The side chains would then be attached *via* an esterification at C₄₅ and a cross coupling across C₂₆-C₂₇.

As outlined previously, we propose to install the C₂₀-C₂₆ piece as the final fragment prior to macrolactonisation, with the C₁₉-C₂₀ bond being constructed *via* a cross coupling. An attractive feature of using a Heck coupling for this purpose would be the simplified terminal functionality, with only an alkene required at the C₂₀ position. Alternatively, Stille or Negishi cross coupling should also afford this bond connection from the respective vinyl stannane or vinyl zinc species.

A Suzuki coupling or Negishi coupling could be employed for the challenging sp²-sp³ coupling to construct the C₁₂-C₁₃ bond. Alternatively, we imagine that a vinyl silane at the C₁₉ position could act as a 'protecting group' for the corresponding vinyl iodide, allowing the construction of the C₁₂-C₁₃ bond *via* such a palladium-catalysed coupling, prior to the revealing of the vinyl iodide in preparation for C₁₉-C₂₀ bond formation.

We envisage that NMR analysis of the individual fragments alone will not provide sufficient insight into the likely natural stereochemistry, due to the flexibility of these fragments and the significant effect of the macrocycle on the conformation of the C₂₁-C₂₄ region. To reduce the total amount of work required to determine the configuration, we aim to synthesise the simplest structure that will provide meaningful stereochemical information to guide the remainder of the synthesis. To this end, we propose the initial construction of a truncated macrocycle (**36**). We anticipate that the side chains should not have a significant effect on the chemical shifts or coupling constants of the macrocycle environments. We therefore hope that the synthesis and spectroscopic analysis of eight stereoisomers of this truncated macrocycle (varying the stereochemistry at the C₂₂, C₂₃ and C₂₄ positions) followed by comparison to NMR spectra for the natural product, will identify the likely stereochemistry of the three unknown macrocycle stereocentres, namely those at C₁₀, C₂₂ and C₂₃. With some confidence in the configuration at these sites, permutations of the C₂₄ stereochemistry could be investigated through a partial synthesis of the C₂₃-C₃₂ side chain. We also considered that the stereochemistry of the linear fragment may influence its ability to macrolactonise, thus eliminating certain diastereomers from consideration at this stage. The truncated synthetic target (**36**) proposed, consequently also simplifies the synthesis of the south-eastern fragment (**39**).

It is critical that the synthesis allows for the late-stage introduction of the sensitive epoxide moiety, which is unlikely to survive any strongly acidic or nucleophilic conditions, as evidenced by the observed epoxide opening with HPLC solvents. To this end, it may need to be introduced as a protected diol and revealed at a late stage. The ketone functionality will also need to be masked (as the corresponding secondary alcohol) for much of the proposed route. Both the presence of two α -chiral methyl groups and the reduction steps required later in the synthesis make the ketone an incompatible functional group for much of the proposed route. Whilst the stereochemistry of this alcohol is therefore inconsequential, installing it with high diastereocontrol will simplify the characterisation of intermediates. This alcohol will require an orthogonal protecting group, to enable the alcohol to be selectively deprotected and oxidised prior to global deprotection of the other hydroxyl groups. The C₂ and C₂₃ alcohols will also need to be selectively deprotected for their respective esterifications.

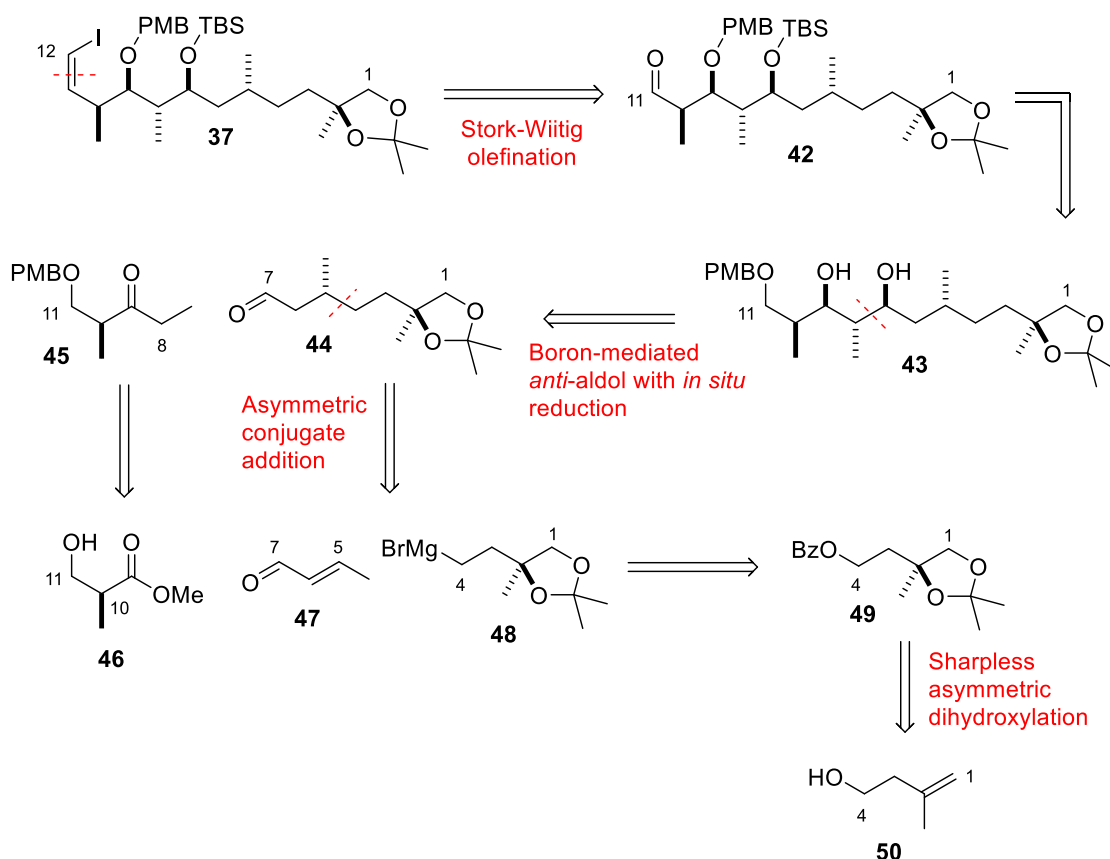
The polyketide derived backbone of the macrocycle naturally lends itself to the use of highly diastereoselective aldol reactions for its construction. We propose that the key stereotriad in the C₁-C₁₂ south-western fragment **37** could be installed using a boron-mediated aldol reaction to form the C₇-C₈ bond, using a chiral ketone building block derived from Roche ester. The isolated C₅ methyl-bearing stereocentre could be installed *via* an enantioselective conjugate addition. The C₁₄-C₁₇

stereotetrad could be set up *via* a glycolate aldol reaction,⁵⁹ followed by stereoselective reduction of the C₁₅ ketone. The unknown stereochemistry in the C₂₀-C₂₆ fragment will need to be installed entirely *via* reagent control, to enable access to all eight possible stereoisomers. With this consideration, a Sharpless epoxidation and crotylation or proparylation are proposed to install the C₂₂, C₂₃ and C₂₄ stereocentres.

Chapter 2: Results and Discussion – Part I

Synthesis of the C₁-C₁₂ Vinyl Iodide

2. 1 Retrosynthesis



Scheme 3: Retrosynthetic analysis for the C₁-C₁₂ fragment

Key to the synthesis of the C₁-C₁₂ fragment is the ability to install a variety of coupling handles at the C₁₂ position, with the C₁₁ aldehyde **42** being targeted as a common intermediate. With one proposal to form the C₁₂-C₁₃ bond *via* a cross coupling, the prerequisite C₁₁-C₁₂ vinyl iodide could be installed *via* a Stork-Wittig olefination,⁶⁰ from this aldehyde. Alternatively, this aldehyde could be converted into the related terminal alkyne using a Seyferth-Gilbert homologation⁶¹⁻⁶³ or Corey Fuchs olefination,^{64,65} to investigate alternative fragment union strategies.

As discussed in **section 1.4**, the C₉ ketone functionality will be masked as a secondary alcohol, necessitating orthogonality in the protecting group strategy. A PMB group will allow selective deprotection in the presence of multiple silyl protecting groups and oxidation of the resulting alcohol.

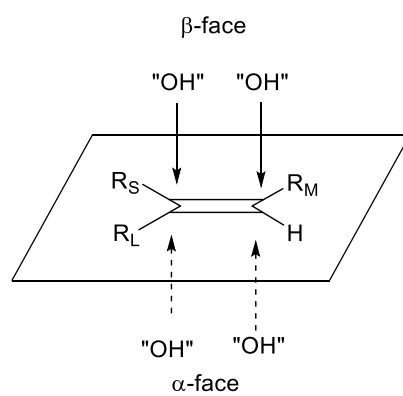


Figure 14: Mnemonic for predicting the facial attack in SAD reactions

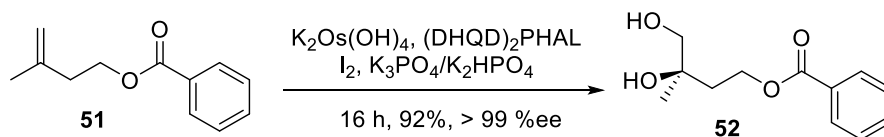
We envisage constructing the key C₇-C₁₀ stereotetrad *via* a boron-mediated aldol reaction, followed by an *in-situ* reduction. This Narasaka type reduction,⁶⁶ should install the 1,3-*syn* diol **43** with high diastereoselectivity, although the absolute stereochemistry at the C₉ position is inconsequential. Ketone **45** can be derived from (*S*)-Roche ester in three steps. We propose that aldehyde **44** could be disassembled into crotonaldehyde and Grignard reagent **48**, making use of an asymmetric conjugate addition. We anticipate the required C₁-C₂ oxygenation arising from a Sharpless asymmetric dihydroxylation on homoallylic alcohol **50**.

2.2 Synthesis of the C₁-C₇ aldehyde

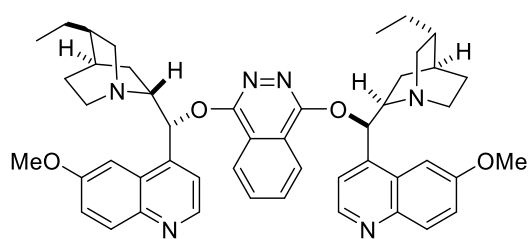
2.2.1 Investigations into Sharpless Asymmetric Dihydroxylations to Install the C₁-C₂ Diol

The first challenge in the synthesis of aldehyde **44** was to install the tertiary hydroxyl group in an enantioselective manner. To this end, a Sharpless asymmetric dihydroxylation was initially investigated.⁶⁷ The following mnemonic (**Figure 14**) can be used to predict which ligand series is required to install the desired stereochemistry. Given the 1,1 disubstitution pattern of the olefin, the methyl group is determined to be the ‘small’ group, hence bottom face attack is required and thus AD_{mix} α should be used. The comparative size of this methyl group means that 1,1-disubstituted alkenes are typically challenging substrates to carry out SAD reactions on, as there is only a small steric difference between the R_S and R_L groups.

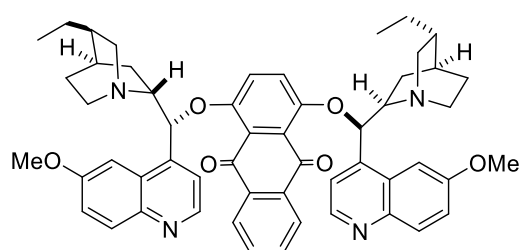
An encouraging report by Jutand⁶⁸ describes modified Sharpless conditions employing iodine as an alternative stoichiometric oxidant and both di- and tri-potassium phosphate as buffers, giving diol **52** from alkene **51** in excellent ee (**Scheme 4**).



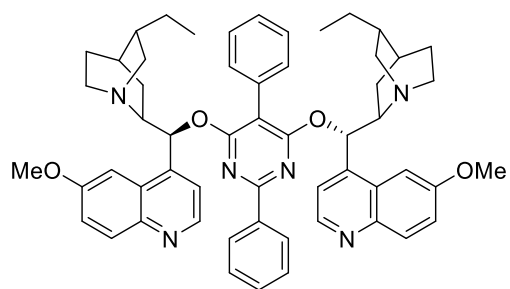
Scheme 4: Reported dihydroxylation conditions by Jutand



(DHQ)₂PHAL, 53



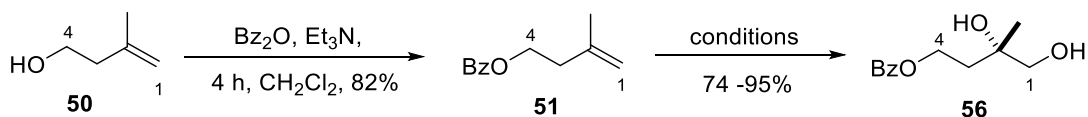
(DHQ)₂AQN, 54



(DHQD)₂PYR, 55

Figure 15: Sharpless ligands used in SAD screen

Esterification of commercial alcohol **50** with benzoic anhydride and triethylamine proceeded in good yield (82%), but the subsequent SAD of alkene **51** under Jutand's conditions (albeit using the pseudoenantiomeric ligand to give the correct patellazole B C₂ configuration) gave a disappointing 18% ee. Issues were encountered with solubility and solvent freezing using *t*-BuOH/H₂O at 0 °C.



Scheme 5: Benzoate protection and dihydroxylation reaction

At this point, more conventional Sharpless dihydroxylation conditions were turned to. Under the standard AD_{mix}α conditions, employing (DHQ)₂PHAL as the chiral ligand, an increased enantiometric excess of 53.4% was observed by HPLC analysis (CHIRALPAC column IA). Whilst this was an advance on the previous conditions, there remained room for improvement.

The use of methane sulfonamide has been reported to improve both conversion rates and enantioselectivities for osmium-catalysed dihydroxylation reactions.⁶⁷ It is claimed that this aids the breakdown of the osmate ester during the catalytic cycle, thus increasing the rate of the catalyst turnover, allowing the reaction to take place at a lower temperature and consequently giving an improvement in ee. Although Sharpless⁶⁷ has suggested that this effect is less pronounced and possibly even detrimental in 1,1-disubstituted systems, it was nonetheless explored for completeness, but accordingly addition of methanesulfonamide led to a diminished ee of 40% (**Table 3, entry 3**).

Entry	Ligand	Temperature	ee %	Yield
1 ^a	(DHQ) ₂ PHAL	0 °C	18	71%
2 ^b	(DHQ) ₂ PHAL	0 °C	53	95%
3 ^c	(DHQ) ₂ PHAL	0 °C	40	90%
4 ^d	(DHQD) ₂ PYR	0 °C	47	97%
5	(DHQ) ₂ AQN	0 °C	85	93%
6	(DHQ) ₂ AQN	-7 °C	86	82%
7	(DHQ) ₂ PHAL	0 °C	34	99%

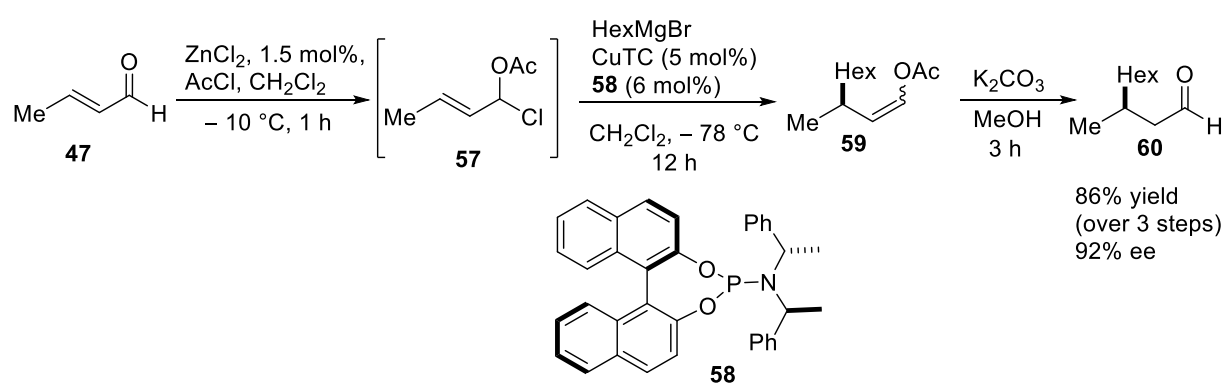
a: I₂ used as the stoichiometric co-oxidant

b: AD_{mix}α used

c: MeSO₂NH₂ additive

d: Enantiomeric product obtained

Table 3: Conditions screens for Sharpless asymmetric dihydroxylation

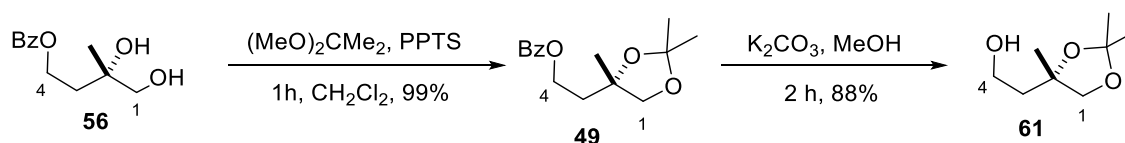


Scheme 6: Enantioselective conjugate addition of a Grignard nucleophile to crotonaldehyde by Feringa

Next, other ligands and temperatures were investigated. (DHQD)₂PYR and (DHQ)₂AQN were chosen for the ligand screen with varying success. Using the (DHQD)₂PYR¹ ligand afforded (the enantiomer of) the desired product **ent-56** in 47% ee (**entry 4**), however (DHQ)₂AQN gave the product diol in a promising 85% ee. All these reactions were run between –2 °C and 0 °C, so in order to investigate the effect of temperature, the reaction with (DHQ)₂AQN was run again at –7 °C. Due to issues with the *t*-BuOH/H₂O solvent freezing, a small quantity of THF was added to reduce the freezing point of the solvent mixture. This temperature change (**entry 6**) did improve the enantiometric excess to 86%, but this improvement is likely to lie within experimental error. Attempts at recrystallisation to improve the ee of the product proved fruitless.

All the enantiomeric excesses of diol **56** were calculated by HPLC analysis, measured against the corresponding racemic diol which was synthesised using standard Upjohn dihydroxylation conditions⁶⁹ (OsO₄, NMO) in 87% yield.

With a suitable method to access diol **56** in good ee established, the subsequent steps in the route could be explored. Diol **56** was successfully protected as the corresponding acetonide **49** with PPTS and 1,1-dimethoxypropane in excellent yield (99%). Benzoyl deprotection then proceeded, under basic conditions, to give primary alcohol **61** in 88% yield (**Scheme 7**).

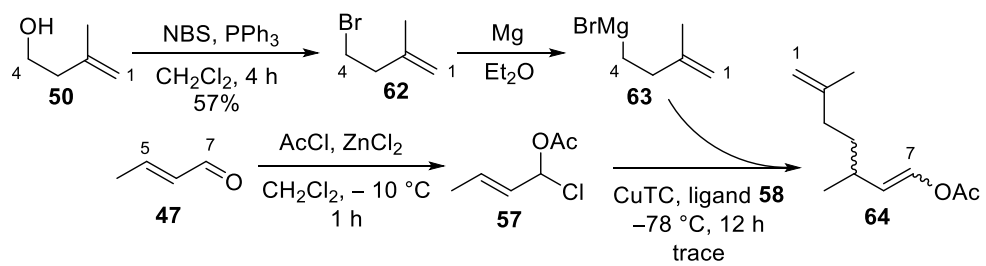


Scheme 7: Protecting group adjustment to give alcohol 61

2.2.2 Asymmetric Conjugate Additions into Crotonaldehyde

We envisaged that the somewhat isolated nature of the C₅ methyl stereocentre would provide a challenge to install. Inspired by studies by Feringa,⁷⁰ an enantioselective conjugate addition of a Grignard reagent such as **63** (**Scheme 8**) into crotonaldehyde catalysed by a chiral phosphoramidite-copper complex was proposed to meet this challenge. This is in effect an S_N2' reaction, rather than a true Michael addition, requiring the chloroacetate to be formed first. Feringa utilises known chemistry to turn aldehydes into α-haloacetates, such as **47** to **57** (**Scheme 6**), a reaction catalysed by zinc chloride.

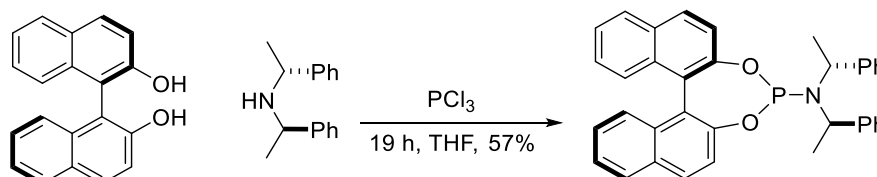
¹ Pseudoenantiomeric ligand used due to availability within our laboratory.



*Scheme 8: Conjugate addition with Grignard reagent **63***

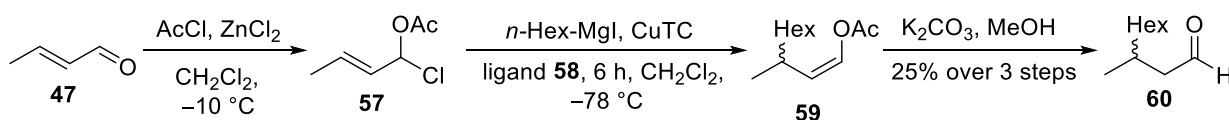
Copper 2-thiophene (CuTC) is then used with a chiral phosphoramidite ligand (**58**) to catalyse the asymmetric S_N2' displacement with a Grignard reagent. The chiral enol acetate **59** can then be easily transformed back into the aldehyde **60** with basic methanol.

Investigations into this proposed route began with synthesis of the requisite phosphoramidite ligands (**Scheme 8**). Chiral phosphoramidite **58** was synthesised in 73% yield, using (*R*)-bis((*R*)-1-phenylethyl)amine, (*S*)-BINOL and PCl_3 in THF.⁷¹



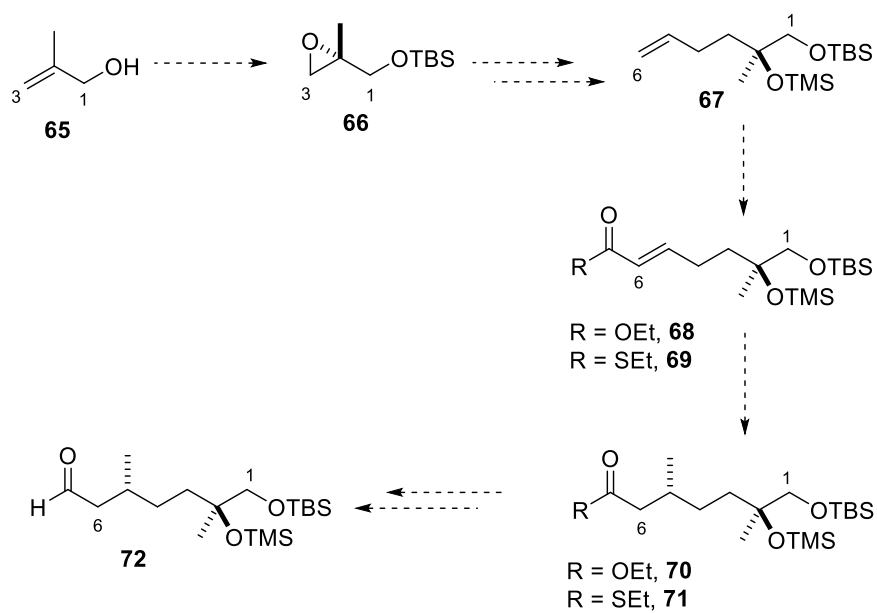
Scheme 9: Synthesis of chiral phosphoramidite ligand 58

With ligand **58** in hand, attention turned to reproducing the results described by Feringa, initially using hexyl magnesium iodide (**Scheme 9**).⁷² Regrettably, this was far from a formality, due to the operationally delicate conditions. The reaction appears to be extremely moisture sensitive, requiring both the zinc chloride to be freshly fused and the crotonaldehyde to be freshly distilled. Temperature is also crucial and with the requirement to add the Grignard solution very slowly, a cryostat must be used over 16 hours. After several attempts, a small amount of product aldehyde **60** was obtained, albeit in a disappointing 25% yield.



Scheme 10: Conjugate addition of an alkyl Grignard nucleophile into crotonaldehyde

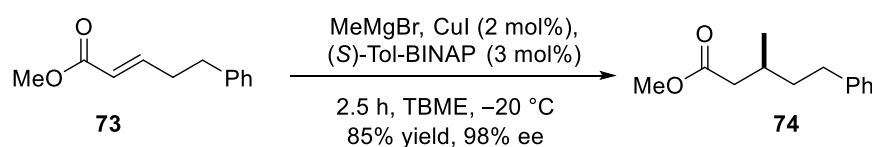
Several attempts were made to generate a more elaborate Grignard reagent. Bromide **62** was prepared from alcohol **50** via an Appel reaction (NBS, PPh_3) in 57% yield, which was then converted into the corresponding Grignard reagent and used immediately in the conjugate addition reaction. Unfortunately, only trace amounts of product **64** were detected (**Scheme 10**). This could either be due to low conversion of the allyl bromide to the Grignard reagent or poor reaction with the chloroacetate owing to the increased bulk of the nucleophile.



Scheme 11: Revised proposal for the synthesis of aldehyde 72

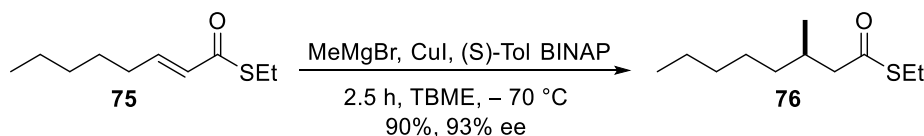
2.2.3 Asymmetric Conjugate Additions of a Methyl Nucleophile

At this juncture, with difficulties in realising the proposed C₄-C₅ bond formation, a new approach to the C₁-C₇ fragment was sought. The installation of the challenging C₅ methyl group was inspired by the work of Loh,⁷³ who reports the asymmetric Michael addition of a methyl nucleophile into unsaturated esters (**Scheme 12**).



*Scheme 12: Conjugate addition with a cuprate nucleophile into **73** by Loh*

Feringa has also shown that conjugate methyl addition can be achieved in good yield and enantioselectivity with α,β -unsaturated thioesters (**Scheme 13**). Due to the increased reactivity of the thioester, these reactions are typically run at lower temperature. Tol-BINAP/CuI or Josiphos/CuBr can be used, but Tol-BINAP/CuI appears to be the more active catalyst system and tolerates a wider range of Grignard reagents, giving good yields and enantioselectivities even for the relatively unreactive MeMgBr.



Scheme 13: Conjugate methyl additions reported by Feringa

Therefore, the strategy remains to configure the C₅ methyl group *via* a conjugate addition, but it will use a more experimentally straightforward variant. Simple oxidation state manipulation of ester **70** or thioester **71** should then give aldehyde **72** ready for the key aldol transformation. The starting materials for the conjugate addition, enoate **68** and thioenolate **69**, could be constructed from alkene **67** *via* a cross metathesis or ozonolysis and HWE olefination.

The proposed route to this alkene (**67**) was the epoxidation of an alkene (**65**), followed by nucleophilic ring opening to give the necessary quaternary hydroxyl stereocentre. Several epoxidation methods were considered including the Shi epoxidation⁷⁴ and a racemic epoxidation followed by a Jacobsen hydrolytic kinetic resolution.⁷⁵ However, with an oxygen required at the C₁ position, the preferred option

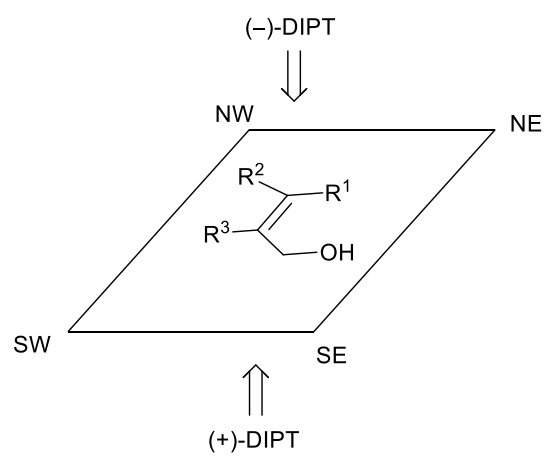
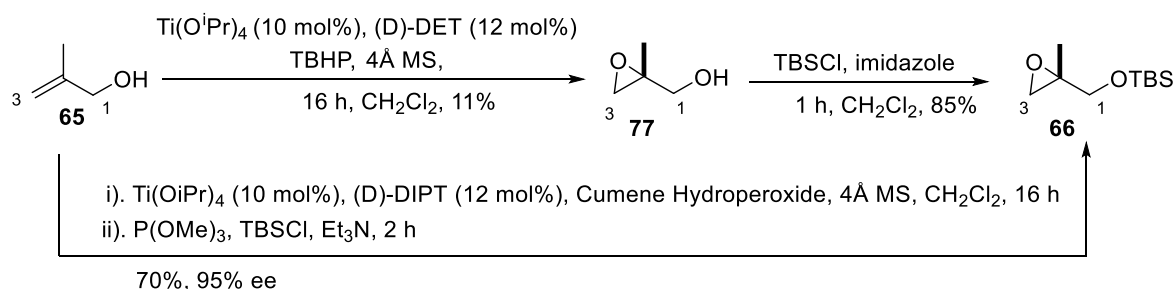


Figure 16: Sharpless mnemonic for asymmetric epoxidation

was to exploit a Sharpless asymmetric epoxidation (SAE)⁷⁶ on allylic alcohol **65**. Therefore, a new route was proposed originating from methallyl alcohol (**Scheme 11**).

Investigations into this revised route began with epoxide formation and opening. Analysis of the Sharpless mnemonic (**Figure 16**) allows for prediction of the correct chiral tartrate ligand to use to obtain the required enantiomer of the epoxy alcohol.⁷⁷

Under standard conditions ($\text{Ti}(\text{O}^i\text{Pr})_4$, (*D*)-DET, TBHP), epoxide **77** was synthesised in 11% yield. Unfortunately, with a free hydroxyl required as a directing group, epoxidation of **65** must take place prior to protection of the primary alcohol. This led to numerous challenges owing to the low molecular weight of the resulting epoxide, notably high water solubility and volatility. Several different work-up procedures were trialled, including iron sulfate, tartaric acid followed by NaOH/NaCl, NaK tartrate, and quenching with anhydrous citric acid. None of these proved successful and a poor yield of epoxide **77** was always obtained.



Scheme 14: Attempted syntheses of epoxide 66

A paper by Sharpless in 1987 described the *in situ* derivatisation of epoxides.⁷⁸ Given the difficulties in isolation of the unprotected epoxy-alcohol, this seemed the most sensible avenue to explore. Sharpless suggests that switching to cumene hydroperoxide as the oxidant and diisopropyl tartrate as the ligand allows lower catalyst loadings to be employed. Trimethyl phosphite is then used to quench the excess cumene hydroperoxide in the second step, followed by *in-situ* protection using TBSCl, which makes the compound easier to isolate and purify. Pleasingly the reaction proved to be highly scalable and, after some optimisation, an overall yield of 70% of epoxide **66** was obtained (**Scheme 14**). The enantiometric excess was determined as 95% ee by HPLC analysis of the corresponding benzoyl protected alcohol, produced by the same methodology (Sharpless epoxidation followed by *in situ* protection with benzoyl chloride).

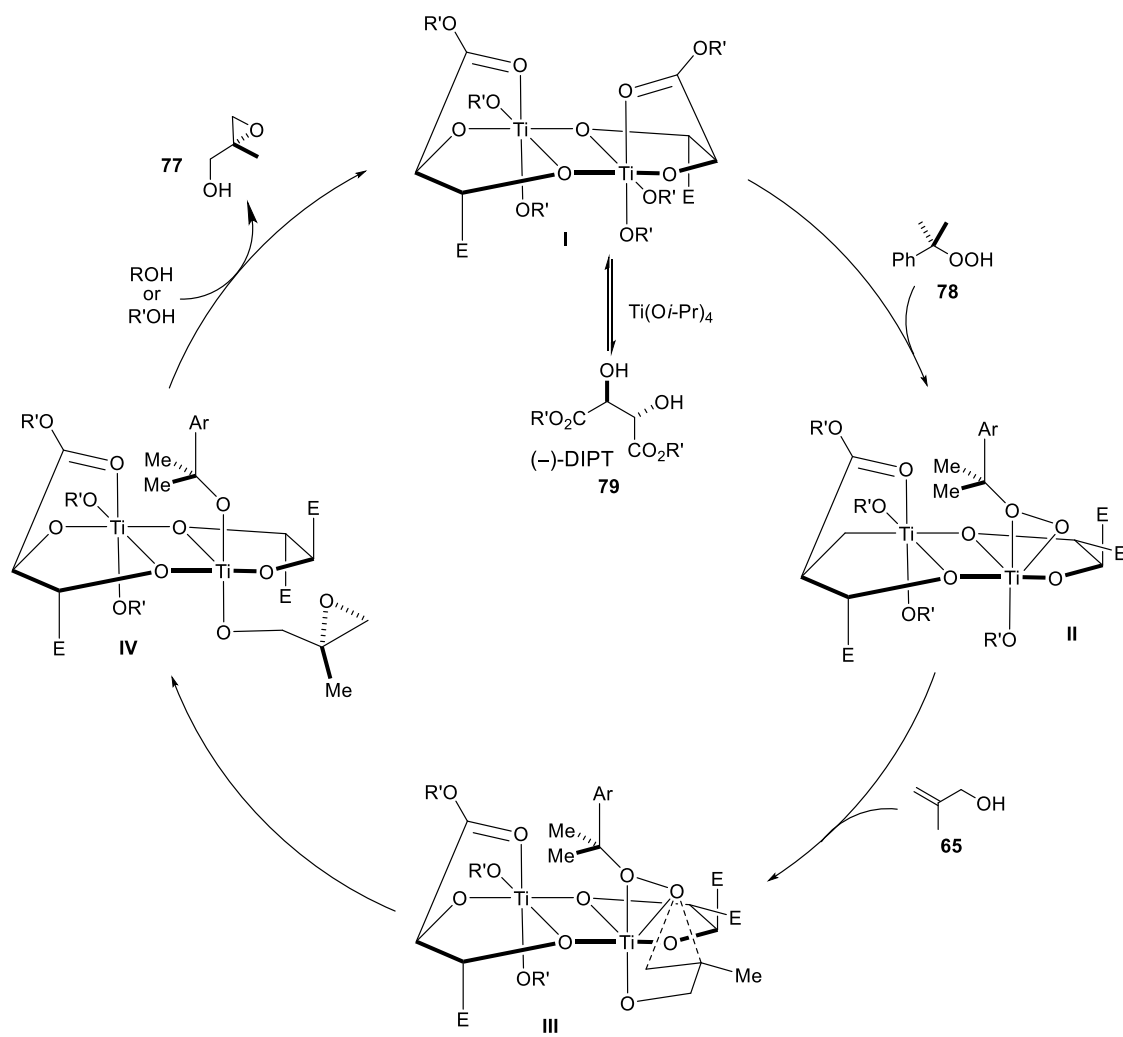
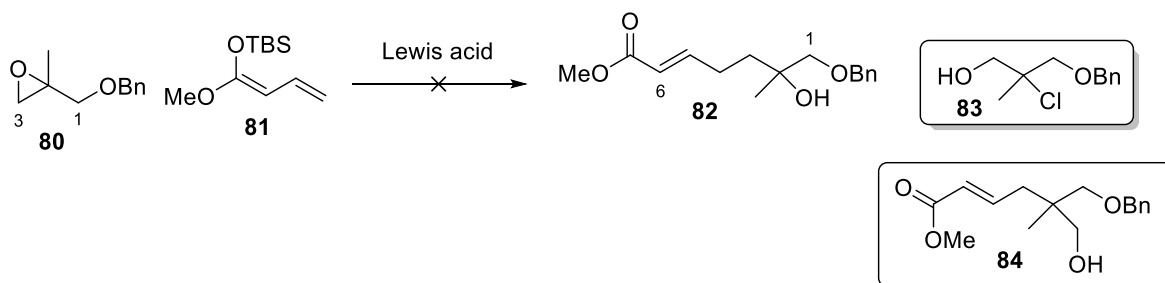


Figure 17: Catalytic cycle for the Sharpless asymmetric epoxidation

The observed enantioselectivity can be explained by consideration of the catalytic cycle shown in **Figure 17**.⁷⁹ Exposure of $\text{Ti}(\text{O}i\text{-Pr})_4$ to the appropriate tartrate ligand results in the reversible formation of dimeric complex **I**. Crucially, the ligands in this complex are able to bind reversibly.⁸⁰ Accordingly, upon the addition of a peroxide source a second complex is generated (**II**), with the peroxide displacing two of the ligands and its facial selectivity determined by the geometry of the chiral ligand. Addition of an allylic alcohol produces a third complex (**III**), wherein the allylic hydroxyl group coordinates to the metal.⁸¹ *Bis*-complexation of the peroxide to the electrophilic titanium species results in a weakening of the peroxide bond, facilitating its transfer to the upper face of the alkene. The steric bulk of the cumene hydroperoxide enhances the enantioselectivity afforded by the chiral environment of the tartrate ligands.⁸² The co-ordinated epoxy alcohol can then be displaced by ligand exchange with either ROH (another allylic alcohol) or $\text{R}'\text{OH}$ ($i\text{-PrOH}$), returning the dimeric titanium complex to the catalytic cycle. The inclusion of molecular sieves ensures the reaction is carried out under strictly anhydrous conditions and ligand exchange with water doesn't occur, which would remove the titanium species from the catalytic cycle.

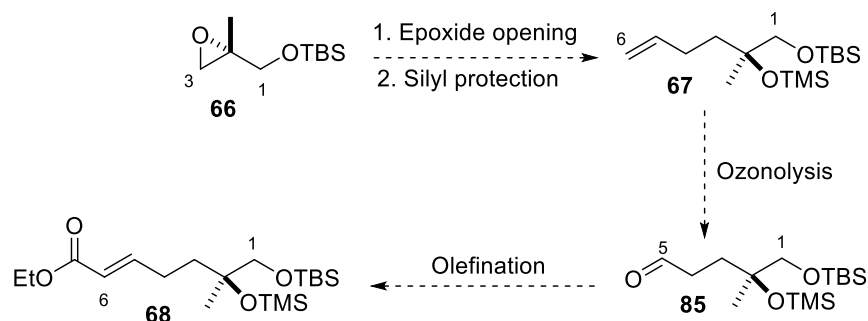
With epoxide **66** in hand and the C_2 stereocentre set with high ee, attention turned to examining the ring opening step (**Scheme 15**). Initial attempts at forming the enoate (**82**) directly from the opening of epoxide **80**² with an extended enolate (**81**) proved unsuccessful. Formation of the requisite silyl ketene acetal from methyl crotonate proceeded in 84% yield, but a small screen of Lewis acids to promote the epoxide opening failed to give any of the desired product. Instead, ring opening at the more hindered end of the epoxide (stabilised by the tertiary carbocation), gave the regioisomeric product **84** (in 32% yield) when BF_3 was used. With chloride containing Lewis acids (TiCl_4 , and $\text{Ti}(\text{O}i\text{-Pr})_2\text{Cl}_2$), dissociation of the halide was followed by nucleophilic attack at the tertiary carbocation to give chloride **83** in 37% and 41% yield respectively.



*Scheme 15: Attempted epoxide opening with silyl ketene acetal **81***

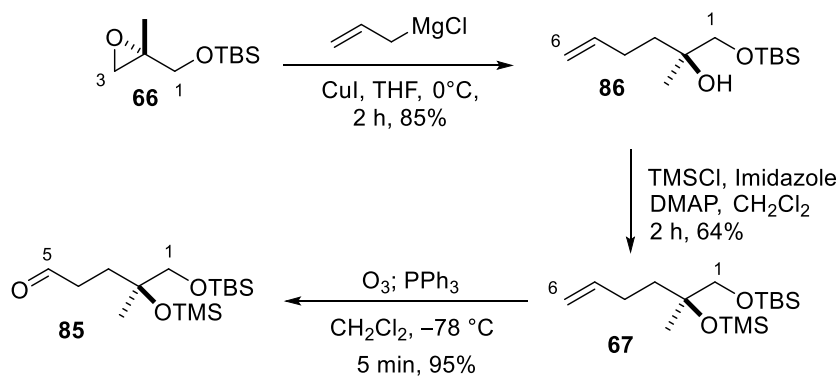
² Racemic epoxide **80** was synthesised using mCPBA for use in initial epoxide opening investigations.

A multi-step route (**Scheme 16**) was, therefore, proposed instead. This would proceed *via* addition of an allyl Grignard reagent to the less hindered end of epoxide **66**. Protection of the newly formed alcohol should give silyl ether **67**. Conversion to the desired enoate (**68**) could proceed *via* ozonolysis of the terminal alkene followed by an HWE olefination.



*Scheme 16: Proposed opening of epoxide **66** and subsequent elaboration into enoate **68***

Preliminary studies began by investigating the epoxide opening reaction. Treatment of epoxide **66** with allyl magnesium bromide led to a mixture of products, obtained in part from bromide opening of the epoxide. Modification of the procedure to use allyl magnesium chloride proved more fruitful, giving alkene **86** as the sole product in 85% yield. The following two steps proceeded smoothly. As shown in **Scheme 17**, treatment of alcohol **86** with TMSCl and imidazole afforded silyl ether **67** in 64% yield, which was then subjected to ozonolysis conditions, giving the desired aldehyde **85** in 95% yield.



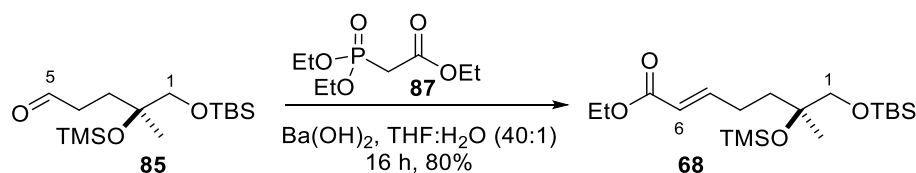
*Scheme 17: Opening of epoxide **66** and subsequent elaboration into aldehyde **85***

Entry	Equivalents of phosphonate	Reagents	R =	Temperature	Product ratio e.g. 89:90	Yield
1	1.5	Ba(OH) ₂	Ph	rt	1:1	86%
2	1.4	NaH	Ph	0 °C	1:0	40%
3 ^a	2.5	LiCl, Et ₃ N	Ph	0 °C	0:1	78%
4	1.8	LiCl, Et ₃ N	Ph	−10 °C	~2.5:1	93%
5	1.2	LiCl, Et ₃ N	Ph	−10 °C	3:1	54%
6	1.8	LiCl, Et ₃ N	Ph	−30 °C	10:1	85%
7	1.8	LiCl, Et ₃ N	Ph	−35 °C	1:0	81%
8	1.8	LiCl, Et ₃ N	Tol	−35 °C	1:0	85%
9	1.8	LiCl, Et ₃ N	Et	−35 °C	1:0	80%

a: MeCN used as solvent. THF used in all other cases.

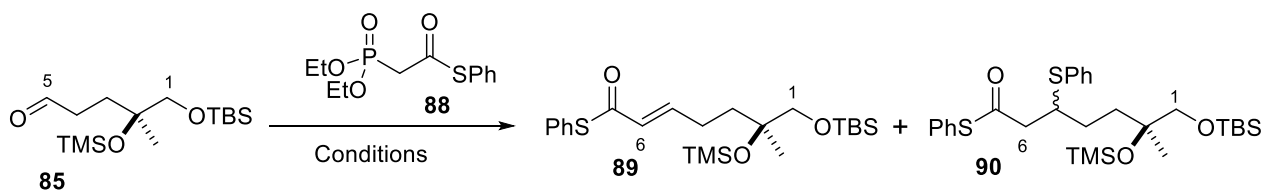
Table 4: Optimisation of thioenoate formation

It was envisaged that two separate HWE olefinations could be used to convert the common intermediate, aldehyde **85**, into enoate **68** and thioenoate **69** respectively. To this end, aldehyde **85** was then reacted with commercial phosphonate **87** under barium hydroxide mediated conditions to give the required enoate (**68**) in 80% yield (**Scheme 18**).



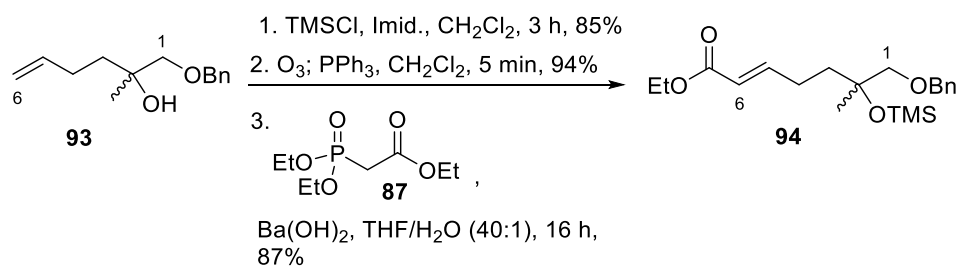
*Scheme 18: Ba(OH)₂ mediated HWE reaction to give **68***

Phosphonate **88** was prepared from diethylphosphonoacetic acid *via* a DCC-mediated thioesterification with thiophenol in 80% yield. In keeping with this route, it was anticipated that the required α,β -unsaturated thioester **89** could be formed *via* a similar barium hydroxide mediated HWE reaction (**Scheme 19**). Unfortunately, using the standard conditions with aldehyde **85** and 1.5 equivalents of phosphonate **88**, an inseparable mixture of products was obtained. The product ratio isolated was roughly 1:1 between the desired product, thioenoate **89**, and the corresponding product **90** from the supplementary 1,4-addition of a thiolate anion into the ensuing thioenoate. Hydrolysis of the remaining phosphonate thioester, potentially with the water used in the solvent mixture, would give free phenyl thiolate anions in solution which could then react with the ensuing thioenoate to give **90** as a 1:1 mixture of diastereomers (**Table 4, entry 1**)

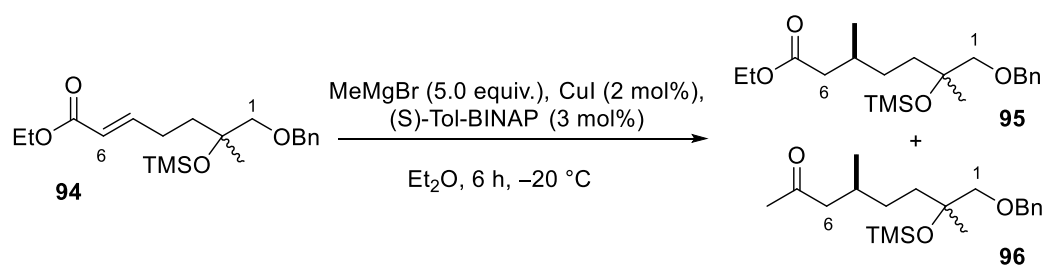


*Scheme 19: Optimisation of HWE olefination to form α,β -unsaturated thioester **89***

With this result, an alternative HWE protocol was sought and the milder conditions detailed by Masamune and Roush were utilised.⁸³ Although a similar outcome was obtained at 0 °C, pleasingly when the reaction was run at a lower temperature (as demonstrated on a similar substrate in the Paterson synthesis towards madeirolide⁸⁴) improved selectivity was observed and at –35 °C (**entry 7**) only the desired product was isolated. The corresponding tolyl and ethyl thioesters were also synthesised in 85% and 80% yield respectively (**entries 8 and 9**)



*Scheme 20: Synthesis of racemic enoate **94***



*Scheme 21: Mixture of products obtained from conjugate addition into enoate **94***

Following the precedent established by Loh,⁷³ it was envisaged that the challenging C₅ methyl-bearing stereocentre could be installed *via* an asymmetric conjugate addition of methyl magnesium bromide into an α,β -unsaturated ester. Methodology using Tol-BINAP and copper (I) iodide has been developed, giving good accessibility to both enantiomers and making use of a readily available catalyst system. Carrying out a solvent screen, Loh established that Et₂O and TBME both gave good results, although with slight improvements using the latter. Loh also discovered that the reaction has a noteworthy temperature dependency. There is a small window around –20 °C for both high yield and selectivity. Below –30 °C a significant decrease in the yield was observed, which was reported to be as a result of formation of a side product, namely the 1,2/1,4 double addition methyl ketone product.

The reaction was initially trialled on a model system. With material available from the epoxide opening in the benzyl ether series, enoate **94** was synthesised over three steps from alkene **93** in 70% overall yield (**Scheme 20**).

However, issues of product mixtures were constantly observed, from the combination of direct and conjugate addition to the enoate (**Scheme 21**). Significant proportions of methyl ketone **96** were consistently isolated. Only a minor effect was observed in varying the copper loadings (**Table 5, entry 2**) and a decrease in the equivalents of the Grignard reagent added resulted in only recovery of starting material (**entry 4**). Slight improvements were observed with a solvent switch to TBME however. Unable to reproduce the results described by Loh and with double addition products consistently observed, this unsatisfactory reaction was abandoned and attention turned to the corresponding reaction on thioenoate **89**.

Entry	equiv. Cul	Product ratio 94:96	Isolated yield
1	0.02	1.1:1	38%
2	0.05	1.2:1	29%
3 ^a	0.02	1.5:1	35%
4 ^b	0.05	n.d.	0%

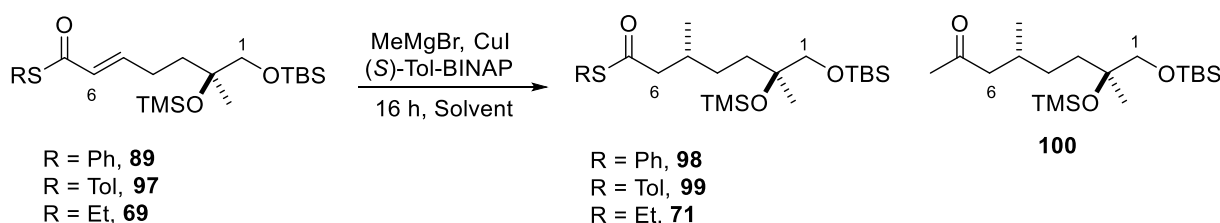
a: TBME used

b: 1.5 equiv. of MeMgBr used

Table 5: Attempted conjugate additions to enoate **94**

Feringa described the thioenoates as a more reactive substrate class, amenable to reaction at lower temperature, so the reactions are typically carried out at $-70\text{ }^{\circ}\text{C}$. No issues of 1,2 vs. 1,4 selectivity have been reported in the literature.

Regrettably, after an extensive screen of conditions, including variation of thioester derivative, copper catalyst loading, Grignard reagent excess, solvent and temperature, it became apparent that this methodology was not compatible with this substrate class (**Scheme 22**). No reaction was ever observed with the tolyl thioester derivative **95** (**Table 6, entries 1-2**). The ethyl derivative **69** was more reactive, but varying ratios of thioester **71** and methyl ketone **100** were produced. Raising the temperature to $-45\text{ }^{\circ}\text{C}$ led to ketone **100** being obtained as the major product (**entry 6**). Numerous attempts were made at repeating the single positive result (**entry 5**), but without success.



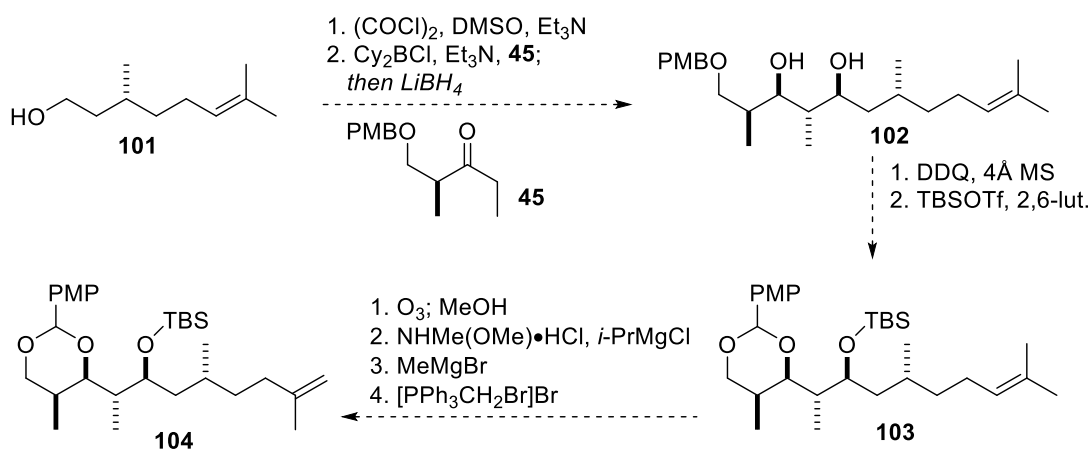
Scheme 22:: Attempted conjugate addition into thioenoates 89, 95 and 69

Entry	R =	Solvent	Temperature	Equiv. CuI	Equiv. MeMgBr	Product ratio e.g. 71:100	Yield
1	Tol	TBME	$-78\text{ }^{\circ}\text{C}$	0.01	4.0	n.r.	0%
2	Tol	TBME	$-78\text{ }^{\circ}\text{C}$	0.05	4.0	n.r.	0%
3	Et	TBME	$-78\text{ }^{\circ}\text{C}$	0.1	4.0	1:1.25 ^a	89%
4	Et	Et_2O	$-78\text{ }^{\circ}\text{C}$	0.1	4.0	n.r.	0%
5	Et	Et_2O	$-78\text{ }^{\circ}\text{C}$	0.1	4.0	15:1	63% ^b
6	Et	Et_2O	$-78\text{ }^{\circ}\text{C} \rightarrow -45\text{ }^{\circ}\text{C}$	0.1	6.0 + 3.0	1:4	72%

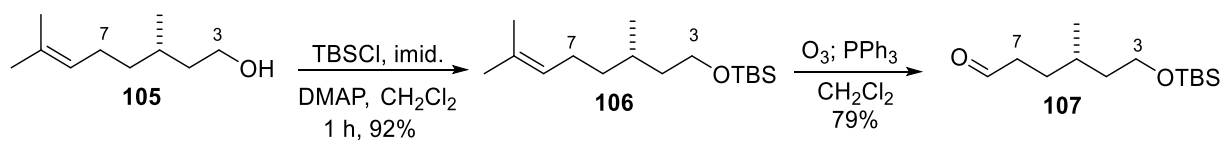
a: Mixture of diastereomers

b: Inseparable mixture with SM (95% brsm). Conditions repeated (x2), but not reproducible.

Table 6: Screen of conditions for conjugate addition into thioenoates 97 and 69



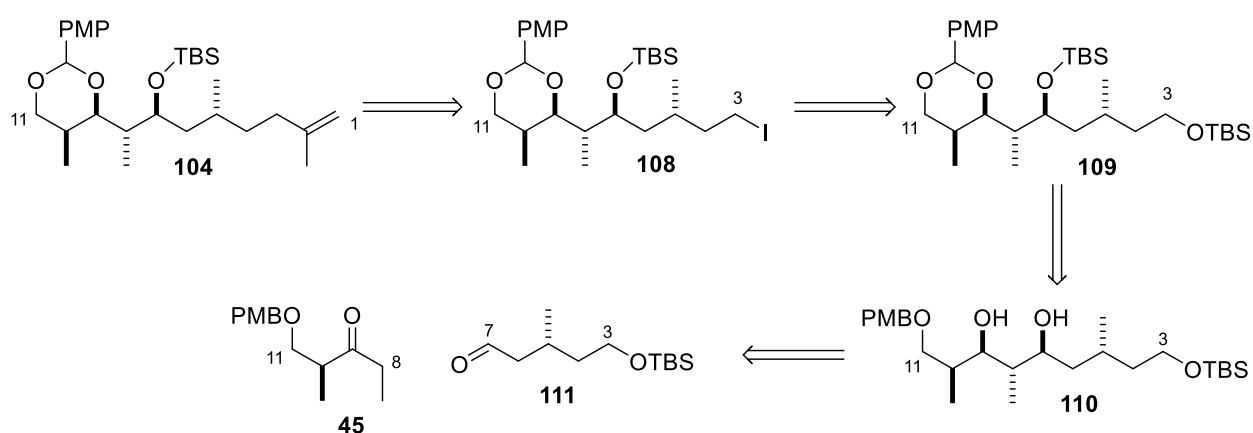
Scheme 23: Proposed alternative route from (+)-citronellol



*Scheme 24: Conversion of (-)-citronellol to aldehyde **107***

2.2.4 Citronellol Dehomologation Studies

At this point, it became apparent that a different approach to the aldol precursor aldehyde would be required. Drawing on our experiences in attempting to install the C₅ stereocentre asymmetrically, it seemed pertinent to look for naturally available sources instead. Citronellol contains an isolated methyl stereocentre, so was proposed as a possible starting material. With a slight modification to the original retrosynthesis; requiring construction of the C₂-C₃ bond at a later stage in the synthesis, the revised target compound became aldehyde **111** (**Scheme 25**). We envisaged that the C₁-C₂ could be installed using a Sharpless asymmetric dihydroxylation, as preceded in **section 2.2.1**.

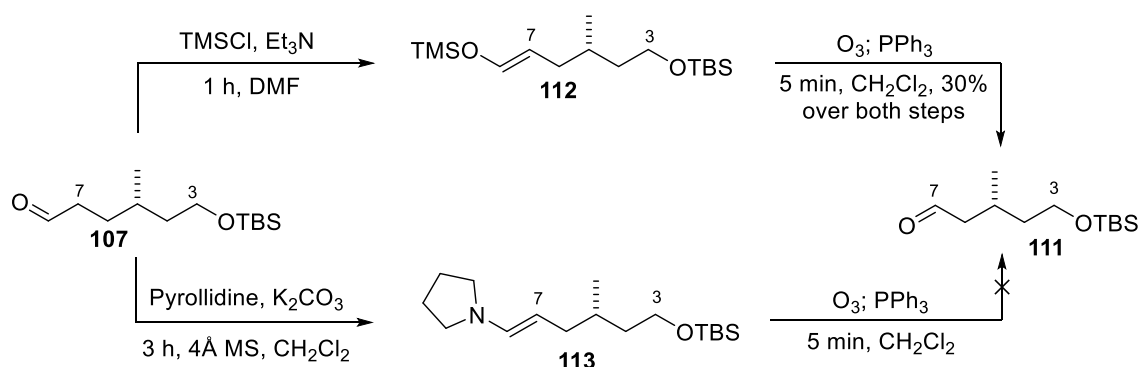


Scheme 25: Revised retrosynthesis for the C₁-C₁₂ fragment

(+)-Citronellol would be the ideal enantiomer to use, since simple oxidation of the primary alcohol should give the corresponding aldehyde (with the correct stereochemistry of the methyl group) suitable for an aldol reaction with ketone **45**. Manipulation of the tertiary alkene later in the synthesis would then provide the requisite terminal C₁/C₂ alkene for dihydroxylation (**Scheme 23**). With (+)-Citronellol considered prohibitively expensive for what would be the starting material in a long synthesis though, a route was proposed originating from (–)-Citronellol instead. The primary alcohol could be protected as a silyl ether to be manipulated into a suitable functional handle for C₂-C₃ bond formation later in the synthesis. Ozonolysis of the alkene would then give aldehyde **107** requiring a single dehomologation to afford aldehyde **111**, in preparation for the aldol reaction with ketone **45**.

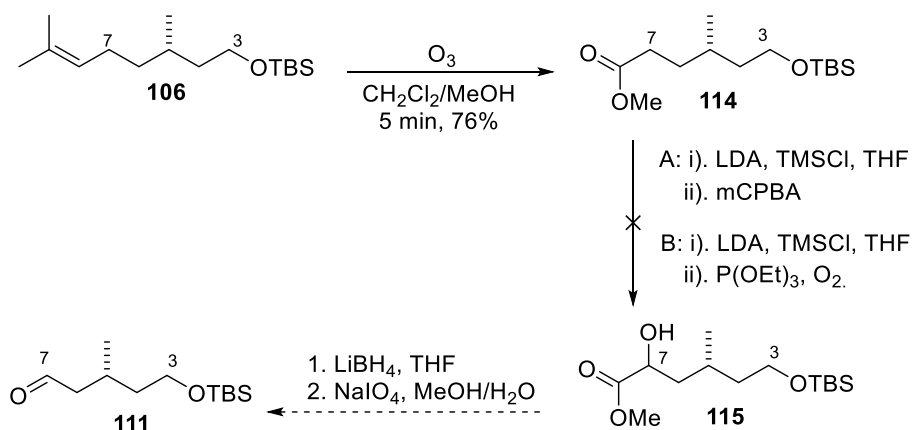
Silyl protection of (–)-Citronellol with TBSCl, DMAP and imidazole, followed by ozonolysis of the trisubstituted alkene, delivered aldehyde **107** in 73% yield over two steps (**Scheme 24**).

It was envisaged that dehomologation of aldehyde **107** could be achieved through formation of the corresponding silyl enol ether or enamine, followed by a second ozonolysis step. Although attempted formation of the TMS silyl enol ether (**112**) with LDA and TMSCl failed to yield any of the silyl enol ether, treatment with TMSCl and triethylamine in DMF led to good conversion. Submission of the crude intermediate to ozonolysis however, provided a disappointingly low yield of the desired aldehyde (30%). Enamine **113** was formed by condensation of aldehyde **107** with pyrrolidine and submitted crude to ozonolysis, but only degradation was observed (**Scheme 26**).



Scheme 26: Attempted dehomologation of aldehyde 107

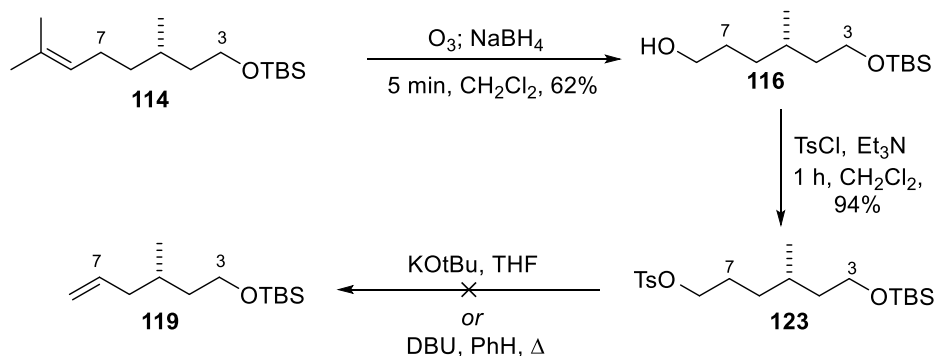
Alkene **106** was then submitted to ozonolysis with oxidative work up, providing ester **114** in 76% yield (**Scheme 27**). It was proposed that oxidation in the α -position (to give **115**) followed by reduction of the ester and periodate cleavage of the ensuing diol should yield the desired aldehyde **111**. Regrettably neither Rubottom conditions,⁸⁵ nor oxidation of the silyl ketene acetal with triethyl phosphite and molecular oxygen⁸⁶ provided the desired alcohol, so this route was not pursued further.



Scheme 27: Attempted α -oxidation of ester 114

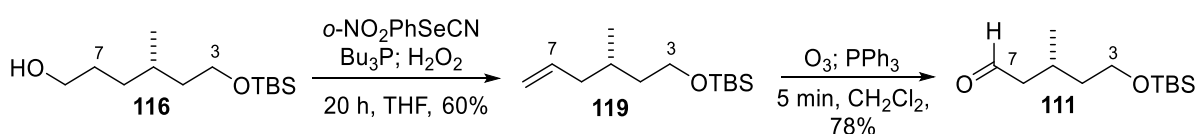


An alternative dehomologation strategy invoking elimination across the C₇-C₈ bond was also attempted. Ozonolysis of alkene **114** followed by a reductive work up gave alcohol **116** in 62% yield (**Scheme 30**). Conversion to the corresponding tosylate (**123**) proceeded smoothly in 94% yield, but unfortunately an attempted E2 elimination with neither potassium *tert*-butoxide nor DBU afforded the requisite alkene **119**, with just starting material being recovered in both cases.



*Scheme 30: Attempted conversion of alkene **114** to alkene **119***

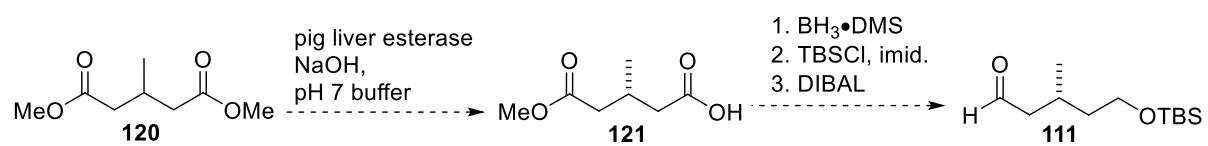
A Grieco elimination⁸⁷ was explored as an alternative dehydration method from alcohol **116**. The proposed mechanism is shown in **Scheme 28**. Reaction of a primary alcohol with *o*-nitrophenylselenocyanate and tributylphosphine gives the organo-selenide **117**. Oxidation of the selenium with hydrogen peroxide to the corresponding selenoxide **118**, then initiates decomposition *via* an E_i elimination to afford the alkene and selenol. This protocol delivered alkene **119** in 60% yield. Ozonolysis of alkene **119** gave the desired aldehyde **111** in 78% yield (**Scheme 31**). Although this synthesis provided useful material to investigate the chemistry further along the route, it was deemed unsatisfactory due to the high step count and use of expensive reagents, especially with this in the longest linear sequence.



*Scheme 31: Conversion of alcohol **116** to aldehyde **111***

2.2.5 Enzyme-mediated Desymmetrisation Reactions

With only modest success from the dehomologation reactions attempted, it became apparent that a new approach to aldehyde **111** was required. Inspired by Fürstner's synthesis of tularin C,⁸⁸ which employs an enzymatic desymmetrisation to furnish both the C₅ and C₁₅ stereocentres, it was envisaged that the same acid intermediate (**121**) could provide access to the desired aldehyde **111** (**Scheme 29**). This route has also recently been utilised in the second-generation Paterson synthesis of aplyronine C.⁸⁹

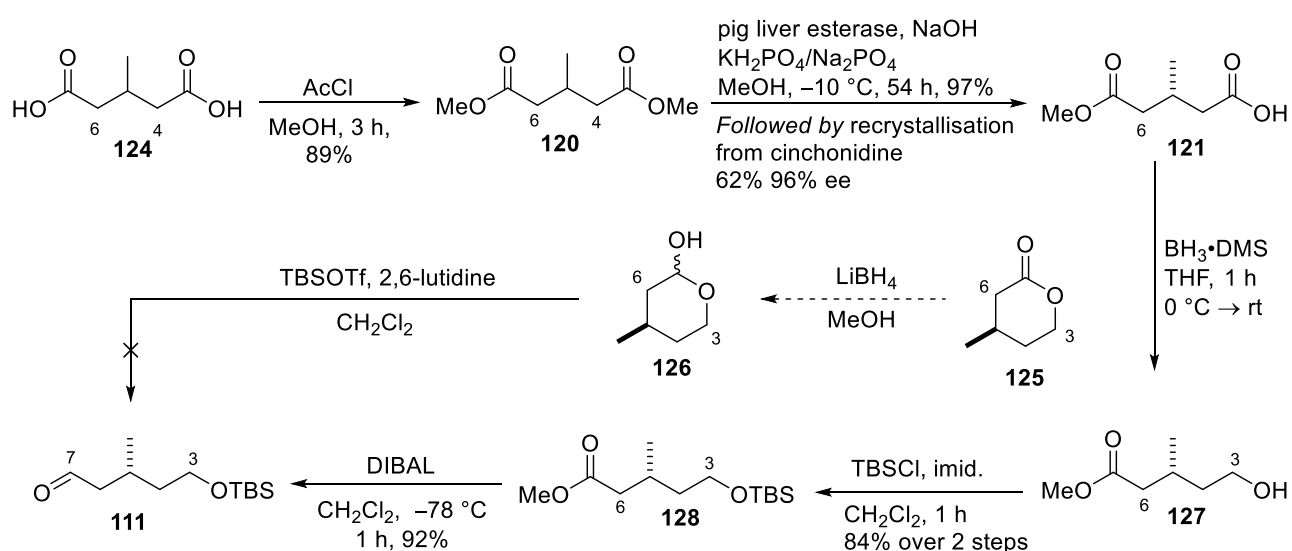


*Scheme 32: Proposed route to aldehyde **111** via an enzymatic desymmetrisation*

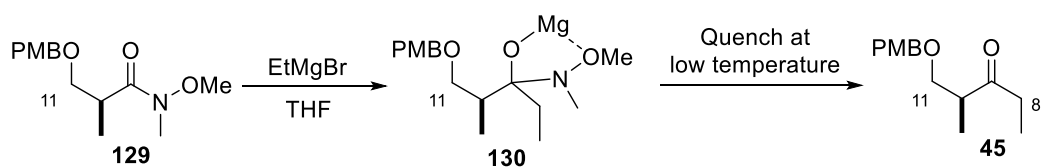
A new route to aldehyde **111** was therefore established. Desymmetrisation of diester **120** would give acid **121**, which could then undergo two chemoselective reductions with an intermediate protection step to give aldehyde **111** (Scheme 32).

Methylation of diacid **124** with acetyl chloride and methanol smoothly delivered diester **120** in good yield (89%) (Scheme 33). Diester **120** was then submitted to the desymmetrisation procedure using pig liver esterase and sodium hydroxide, under buffered conditions, maintaining a pH of between 6.5 and 7.5. Recrystallisation of the crude material as its cinchonidine salt furnished the product with excellent enantiopurity (96% ee) and good yield (60%). The acid moiety was then selectively reduced to alcohol **127** with borane dimethyl sulphide complex. The standard work up procedure of azeotrope with methanol unfortunately led to significant quantities (20-40%) of lactone side product **125** being isolated. It was envisaged that the corresponding lactol **126** (provided by Mike Housden) might lead directly to aldehyde **111** under silyl protection conditions, but unfortunately was not successful.

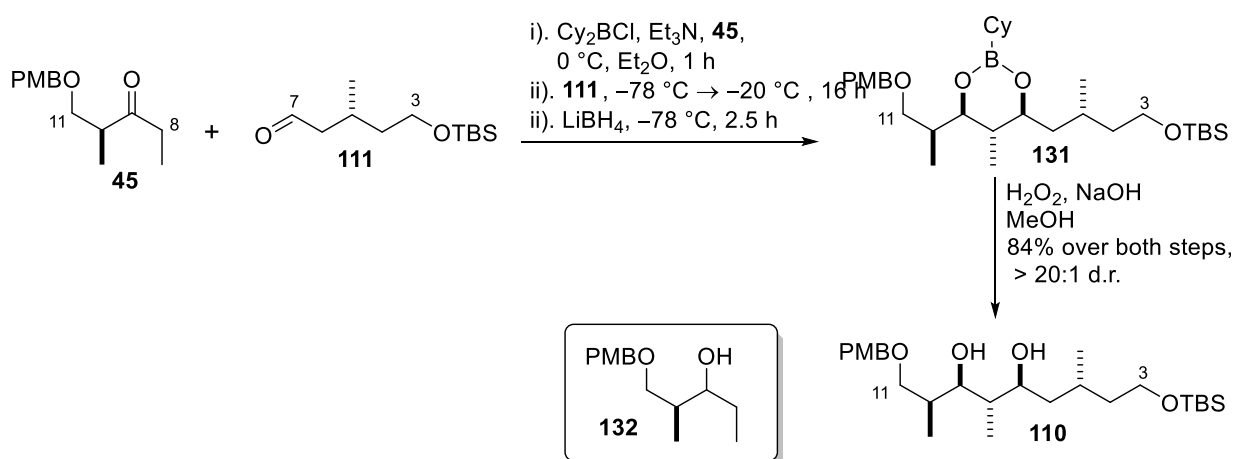
Gratifyingly though, switching to an aqueous work up procedure under basic conditions predominantly eliminated formation of the lactone (to around 2%). Due to its volatile nature, alcohol **127** was just purified through a short plug of silica and submitted directly to the silyl protection with TBSCl and imidazole, giving silyl ether **128** in 84% yield over both steps. Ester **128** was then smoothly reduced to aldehyde **111** in excellent yield (92%). Maintaining a reaction temperature of $-78\text{ }^{\circ}\text{C}$ and careful monitoring of the reaction time and equivalents of DIBAL, ensured over reduction to the corresponding alcohol was kept to a minimum.



Scheme 33: Enzymatic desymmetrisation of diester **120** and subsequent elaboration to aldehyde **111**



Scheme 34: Mechanism for the addition of a Grignard reagent into Weinreb amide **129**

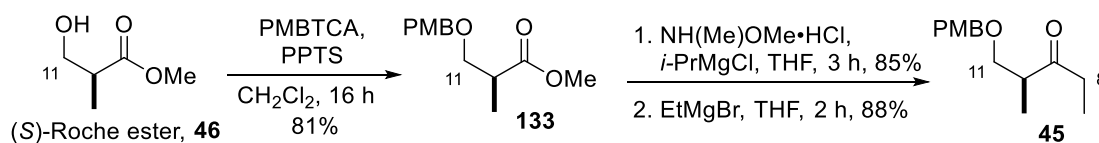


Scheme 35: Boron-mediated anti-aldol with in situ reduction

2.3 Completion of the C₁-C₁₂ Fragment

2.3.1 Boron-mediated anti-Aldol with *in situ* Reduction

With aldehyde **111** in hand, attention turned to the construction of the stereotetrad, *via* a boron-mediated *anti* aldol with *in-situ* reduction. Ketone **45** was synthesised following well established methodology (Scheme 36).⁹⁰ (*S*)-Roche ester (**46**) was protected as PMB ether **133** with PMBTCA and PPTS, and the product converted to Weinreb amide **129** with (*N,O*)-dimethylhydroxylamine hydrochloride in the presence of isopropyl magnesium chloride. Addition of ethyl magnesium bromide then gave ethyl ketone **45** in 61% yield over the three steps. The use of a Weinreb amide prevents over addition of the Grignard nucleophile (Scheme 34). Tetrahedral intermediate **130** is stabilised at low temperature by chelation to the magnesium from the methoxy group. Quenching at low temperature ensures this intermediate doesn't break down in the presence of excess Grignard reagent, delivering the ketone selectively and none of the corresponding tertiary alcohol.



Scheme 36: Synthesis of ethyl ketone **45**

With both ketone **45** and aldehyde **111** in hand, the boron mediated aldol reaction was investigated. Enolate formation at 0 °C using a bulky Lewis acid (dicyclohexylboron chloride) and an unhindered amine base (triethylamine) selectively gave the (*E*)-enolate, which was then cooled to –78 °C prior to the addition of aldehyde **111**. After four hours at this temperature and 16 hours at –20 °C, the reaction mixture was recooled to –78 °C before the addition of LiBH₄, affording the reduced aldol adduct **110** in excellent yield (84%, Scheme 35).

It was found however, that the product, diol **110**, and the secondary alcohol (**132**) derived from the reduction of excess ketone, were inseparable by flash column chromatography. A modified purification procedure was therefore developed, whereby the reduced aldol adduct was kept as the boronate ester (**131**) during the first round of chromatography, thereby allowing separation from the unwanted byproduct. At this point, the oxidative work up with sodium hydroxide and hydrogen peroxide was carried out, before a second round of chromatography provided the clean product.

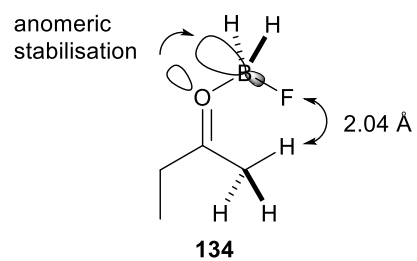


Figure 18: The lowest energy structure for BH_2F complexed to butanone

The selective boron-mediated enolization of ethyl ketones has been well documented in the literature.⁹¹ Small alkyl groups on the boron Lewis acid (e.g. *n*-butyl), a good leaving group (e.g. triflate) and a bulky base (e.g. DIPEA) will selectively give the (*Z*)-enolate. The opposite conditions to this however; bulky ligands on the boron (e.g. cyclohexyl), a poor leaving group (e.g. Cl) and a less sterically demanding base (e.g. triethylamine) have been shown to give the (*E*)-enolate selectively. The rationale for this difference involves both steric and electronic factors. Molecular modelling studies by Paterson and Goodman on the complexation of dialkyl boron fluorides with butanone, indicated that the boron preferentially lies on the same side of the carbonyl as the methyl group rather than the ethyl group (**Figure 18**). The fluoride also adopted a position eclipsing the carbonyl, with the H-F interatomic distance found to be less than the sum of their Van der Waals radii. This can be explained by an anomeric effect, whereby the uncomplexed carbonyl lone pair can donate electron density into the B-F σ^* . A separate NMR study by Forsén with BF₃ and butanone had also suggested that the boron was disposed to favouring the methyl side. A shielding effect of 2.0 ppm at the methyl carbon was observed, indicating a partial build up of negative charge at this site. Moreover, with unsymmetrical ketones such as **45**, the boron will favourably complex to the lone pair on the same side of the carbonyl as the less substituted α -centre (Me>Et>*i*-Pr), i.e. that best able to stabilise the development of negative charge. With the requirement for the enolized proton to be perpendicular to the carbonyl, i.e. for good overlap between the C-H σ molecular orbital and the C-O π^* , the enolate geometry formed will be determined by the relative geometries of the second proton and the methyl group. The bulkier dicyclohexyl ligands force the methyl group to be *trans* to the carbonyl (**Figure 19**).

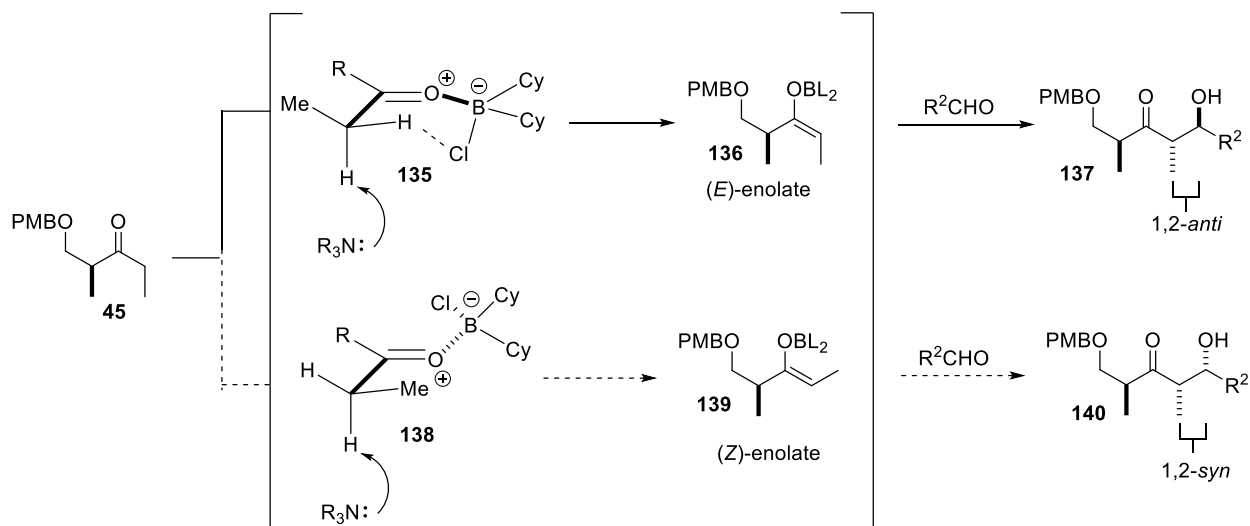


Figure 19: Selective formation of (*E*)-enolates with bulky boron ligands, poor leaving groups and unhindered tertiary amine bases.

DFT analysis by Goodman and Paton⁹² has proposed that the aldol reaction between enolate **136** and an aldehyde proceeds *via* a boat like transition state (**TS-141**). A formyl hydrogen bond between the PMB protected ether lone pair and the aldehydic proton provides a stabilising interaction. This also enhances the preference for the aldehyde substituent to adopt an equatorial position. The α -methyl stereocentre then dictates the π -facial selectivity of the enolate. In the favoured transition state, 1,3-allylic strain is minimised by placing the methyl group away from the transition state and the corresponding proton eclipsing the enolate double bond. The high selectivity for **TS-141** over **TS-143** can be attributed to the short B-O bond length, leading to a compact transition state and accentuating these steric effects. Consequently, the 1,2-*anti*, 1,4-*syn* product is strongly favoured over the 1,2-*anti*, 1,4-*anti* product. (**Figure 20**). With the aldehyde in question containing only a β -chiral centre and no α -chiral centre, the influence of this stereocentre should be insignificant.

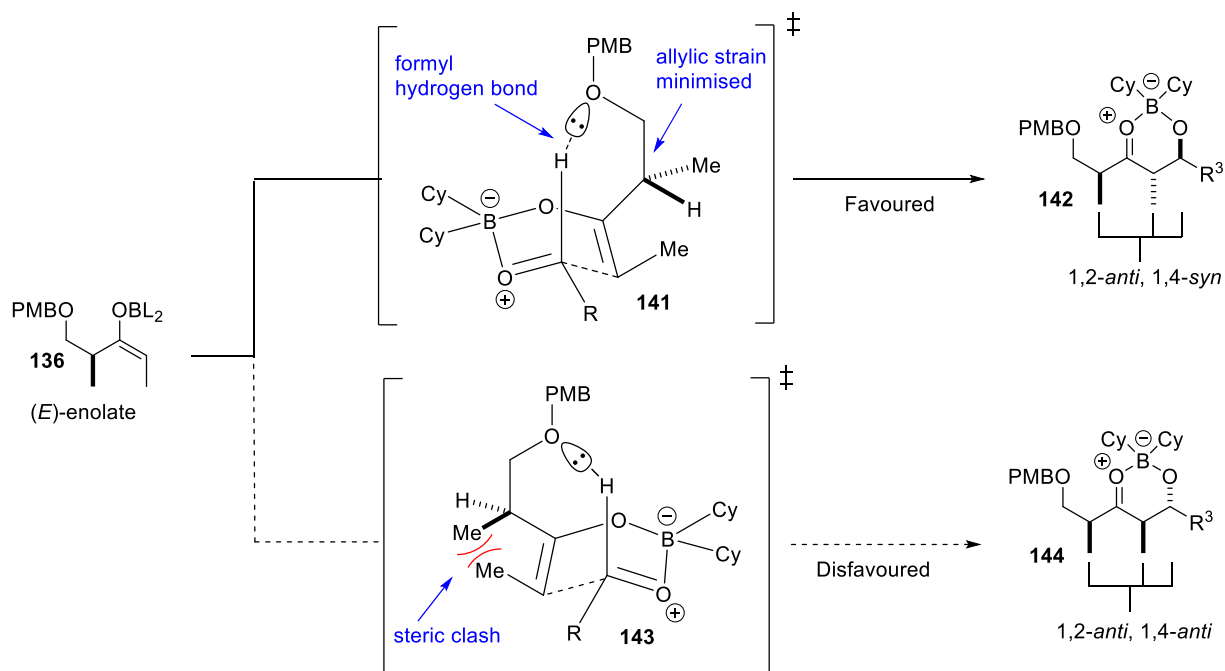


Figure 20: Rationale for facial selectivity in boron-mediated anti-aldol reactions

The C₉ oxygenated stereocentre in patellazole B exists in the ketone oxidation state, but due to the presence of two α -chiral stereocentres and a reduction step later in the synthesis, it seemed prudent to mask this ketone as the corresponding protected secondary alcohol, which could be selectively deprotected and oxidised during the endgame. Taking this into consideration, the absolute stereochemistry of this secondary alcohol is inconsequential, and can be generated *via* the *in-situ* reduction of aldol adduct **153**. Although the same transformation (albeit giving the opposite stereochemistry) could be afforded by an Evans-Saksena or Evans-Tischenko reduction, the reduced step count is clearly an attractive feature of this Narasaka-type approach. With the boron already

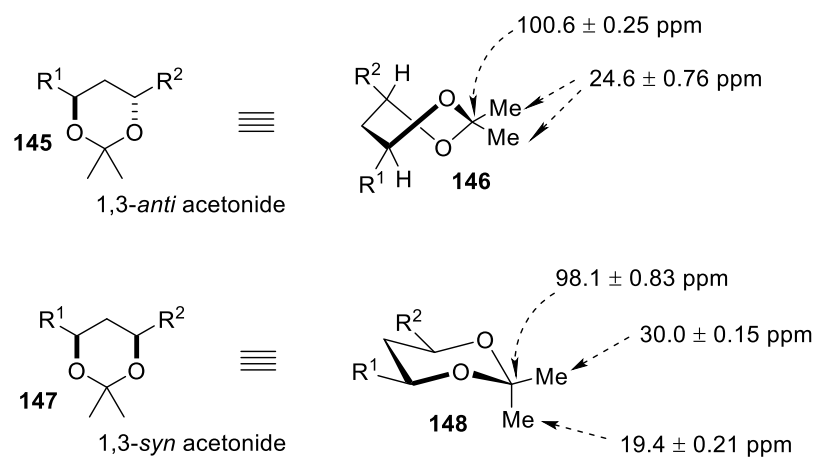
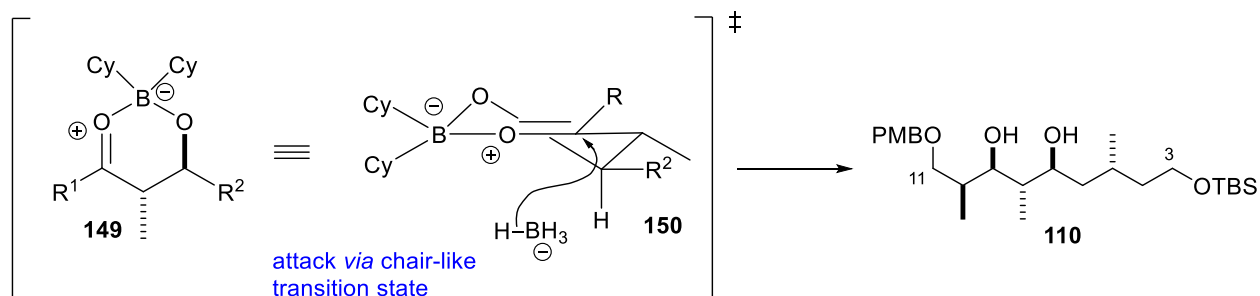


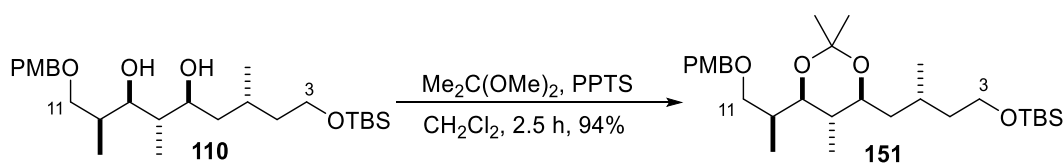
Figure 21: Characteristic ^{13}C resonances for 1,3-*anti* and 1,3-*syn* acetonides (literature values)

chelated between the alcohol and adjacent ketone, the aldol adduct adopts a half-chair conformation, placing the larger substituents in equatorial positions. Attack of the hydride is favoured from the lower face, since this results in the transition state adopting the lower energy chair-like conformation (as opposed to the higher energy twist boat conformation). This follows the Fürst-Plattner rule of diaxial ring opening (**Scheme 37**).⁹³



Scheme 37: Stereoselective in situ 1,3-syn reduction

The relative stereochemistry of the diol was established by formation of the corresponding acetonide (**151**) with 2,2-dimethoxypropane in the presence of PPTS (**Scheme 38**). Analysis of the ¹³C NMR shifts by the method described by Rychnovsky⁹⁴ and coworkers allows for differentiation between *syn*- and *anti*-acetonides. To minimise 1,3-diaxial strain, the *anti*-acetonide will adopt a twist boat conformation, placing the two methyl groups in similar pseudo-equatorial environments. The *syn*-acetonide however will adopt a chair conformation, allowing both side chains to be positioned equatorially. This places one methyl group equatorial and one axial, giving them significantly different environments (**Figure 22**). Diagnostic ¹³C NMR shifts of 19.5, 30.1 and 97.6 ppm for the acetonide carbons served to confirm the *syn* relationship between the C₇ and C₉ alcohols.



Scheme 38: Formation of acetonide 151

The absolute configuration of the diol was confirmed by Mosher ester analysis.^{95–97} Aldol adduct **153** was isolated without *in situ* reduction. The C₇ alcohol was converted to the corresponding Mosher esters, from the appropriate Mosher acids, using Steglich esterification conditions (DCC, DMAP, **Scheme 39**).⁹⁸

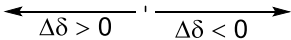
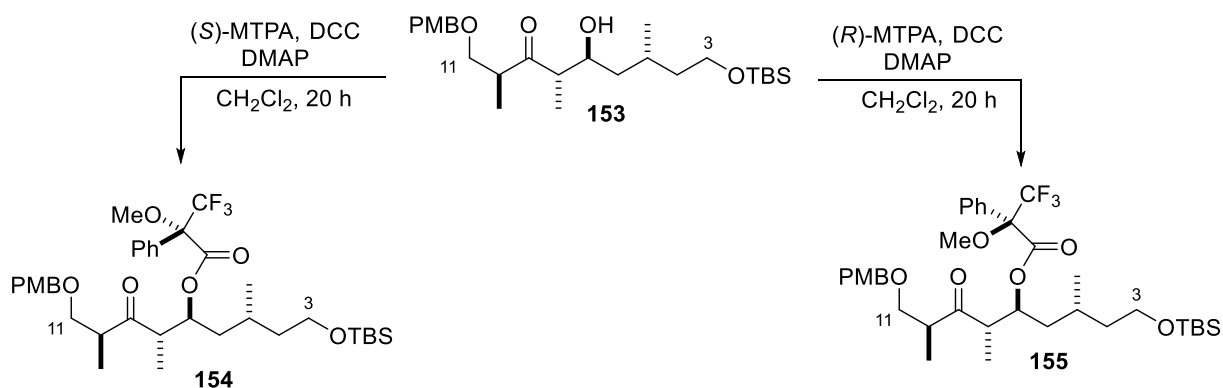


Table 7: Mosher ester analysis for aldol adduct **153**

Scheme 39: Synthesis of Mosher esters **154** and **155** from aldol adduct **153**

The preferred conformation for Mosher esters to adopt in solution, places the carbinol proton, MTPA carbonyl and trifluoromethyl group in the same plane. The phenyl ring has a diamagnetic shielding effect on protons in its vicinity, causing a lowering in their chemical shift (**Figure 22**). In the (*S*)-MTPA ester, those protons in the β' , γ' and δ' positions will therefore have upfield shifts relative to those in the β , γ and δ positions (which lie closer to the methoxy substituent). The opposite will be true however in the (*R*)-MTPA ester case. Comparison between these two cases by subtraction of the (*R*)-MTPA ester shifts from those for the (*S*)-MTPA ester allows determination of the configuration at the carbonyl centre. Assignments of proton environments with $\Delta\delta < 0$ belong on the left-hand side of the MTPA plane (from the perspective of the trifluoromethyl group), whereas those with $\Delta\delta > 0$ belong on the right-hand side. Analysis of the ^1H NMR data from the (*R*)-MTPA and (*S*)-MTPA esters (**Table 7**) gave confirmation that the configuration of the C_7 stereocentre had been set as *7S* as predicted from the stereochemical models for the Cy_2BCl mediated aldol reaction.

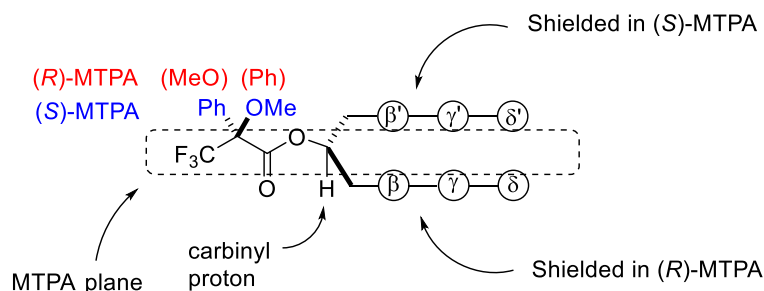
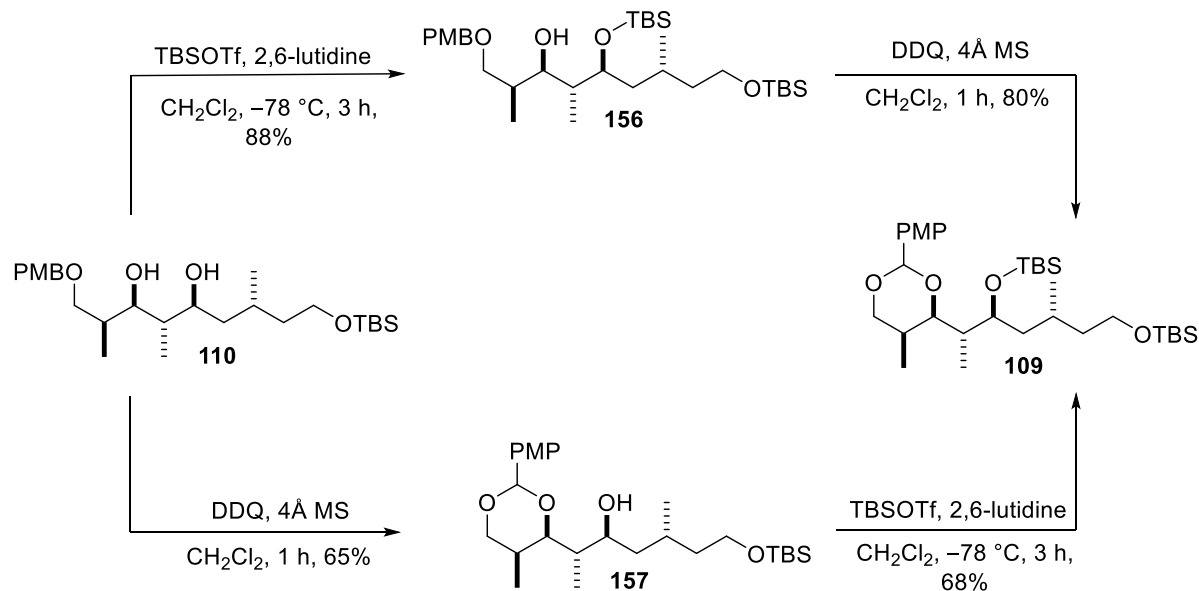


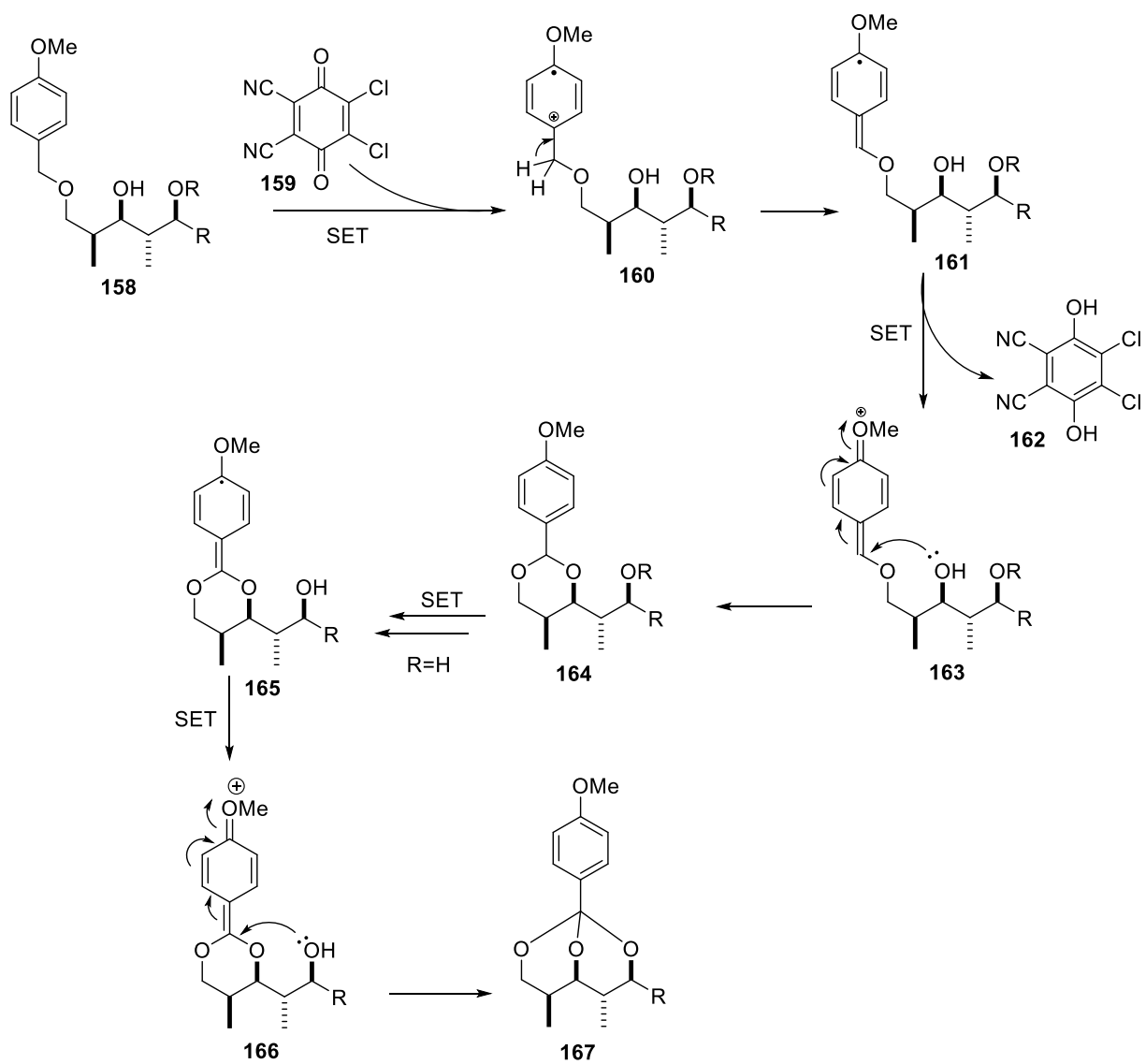
Figure 22: Mosher ester conformation and analysis

2.3.2 Differential Protection of Diol **110**

With aldol adduct **110** in hand, attention turned to how best to differentially protect diol **110**. Two routes were considered for the transformation to compound **109**, in which silyl protection of the C₇ alcohol and PMP-acetal formation between C₉ and C₁₁ could take place in either order. Initial attempts were made to form PMP acetal **157** from PMB ether **110**, but yields were modest at best (65%). Varying amounts of the equivalent ortho-ester were formed as an unwanted side product. Silyl protection of the remaining free alcohol again proceeded in a somewhat disappointing 68% yield (**Scheme 40**).

With this route deemed unsatisfactory, the order of protection was reversed. Pleasingly, diol **110** was selectively protected as the C₇ silyl ether (**156**) with TBSOTf and 2,6-lutidine in 88% yield. Careful monitoring by TLC allowed the reaction to be quenched before significant quantities of the *bis*-silyl protected product were formed. This positive result would appear to confirm that the C₇ alcohol is the less sterically hindered. Conveniently, with this alcohol protected, we would postulate that the remaining free C₉ alcohol is sufficiently more hindered as to prohibit *bis*-protection. With only one free alcohol remaining, treatment of PMB ether **156** with DDQ under strictly anhydrous conditions (freshly powdered and microwaved molecular sieves), smoothly delivered PMP acetal **109** in 80% yield as a 1.4:1 ratio of diastereomers at the acetal.

Scheme 40: Differential protection of diol **110**

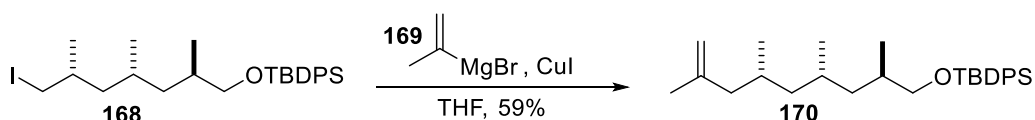


Scheme 41: Mechanism for the DDQ induced PMP acetal formation and over-reaction

The mechanism of the PMP acetal formation proceeds as shown in **Scheme 41**. Treatment of the PMB ether with DDQ effects a single electron transfer giving radical cation **160**, with the radical stabilised adjacent to the methoxy group. Deprotonation at the benzylic position, followed by a second single electron transfer generates oxonium species **163**. Under strictly anhydrous conditions, this is trapped by an internal nucleophile, furnishing PMP acetal **164**. Reaction of the PMP acetal with a second equivalent of DDQ results in the formation of oxonium species **116**, which, in the presence of a second free alcohol, can form orthoester **167**.

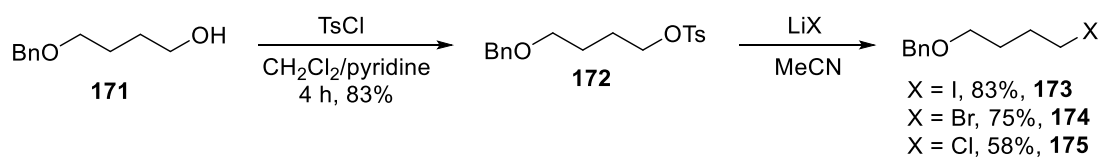
2.3.3 Initial studies into C₂-C₃ Coupling Strategy

At this junction, it seemed opportune to construct the C₂-C₃ bond and install the terminal olefin in preparation for C₁/C₂ dihydroxylation. Surveying the literature, we identified a paper by Nagumo, describing the displacement of halide **168** with a soft nucleophile; namely the cuprate derived from 2-bromopropene (**Scheme 42**).



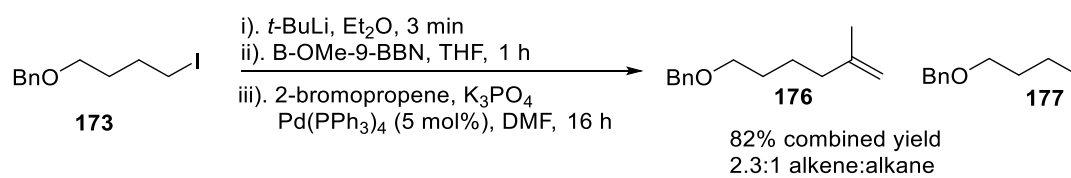
*Scheme 42: Cuprate displacement of iodide **168** by Nagumo*

To investigate this methodology, and others making use of an alkyl halide as a functional handle, a series of model substrates were synthesised as detailed in **Scheme 43**. Alcohol **171** was converted into the corresponding tosylate **172**, which was then displaced with a range of lithium halide salts to form model iodide **173**, bromide **174** and chloride **175** in 83, 75 and 58% yield respectively.

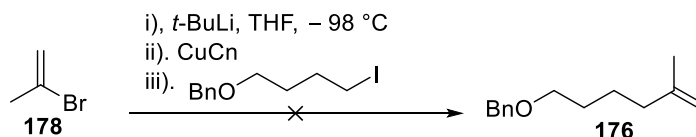


*Scheme 43: Synthesis of model halides **173**, **174** and **175***

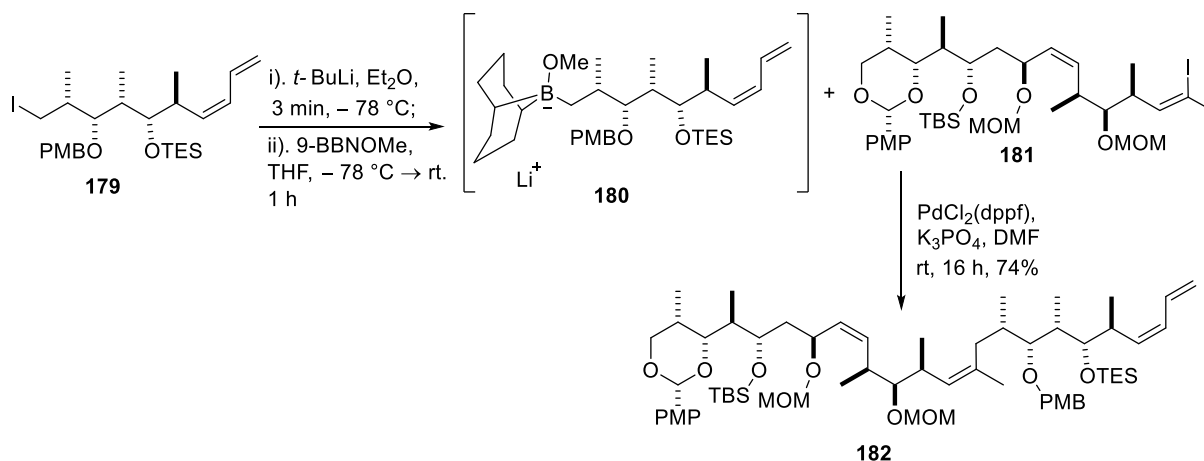
Disappointingly, the reaction led only to recovery of the starting material, when attempted on both the iodide and bromide (**Scheme 45**). The use of freshly dried copper (I) iodide and copper (I) cyanide did not lead to an improvement in reactivity. Attempts at cuprate formation were made *via* both the Grignard reagent and organolithium species derived from 2-bromopropene, but neither delivered any desired displacement product. Successful lithiation was confirmed by addition of the vinyl lithium intermediate into benzaldehyde.



Scheme 44: Model system to investigate in-situ Suzuki coupling

Scheme 45: Attempted displacement of iodide **173** with a propenyl cuprate

Marshall's synthesis of Discodermolide, makes use of a lithiation-borylation-Suzuki coupling sequence to construct the C₁₄-C₁₅ bond. Alkyl iodide **179** was transformed into boronate **180** via a lithium-halogen exchange with *t*-BuLi and subsequent trapping of the intermediate alkyllithium with *B*-methoxy-9-BBN. An *in-situ* Suzuki coupling with vinyl iodide **181** as the coupling partner, catalysed by Pd(dppf)Cl₂, then gave the trisubstituted olefin (**182**) in 74% yield (Scheme 46).



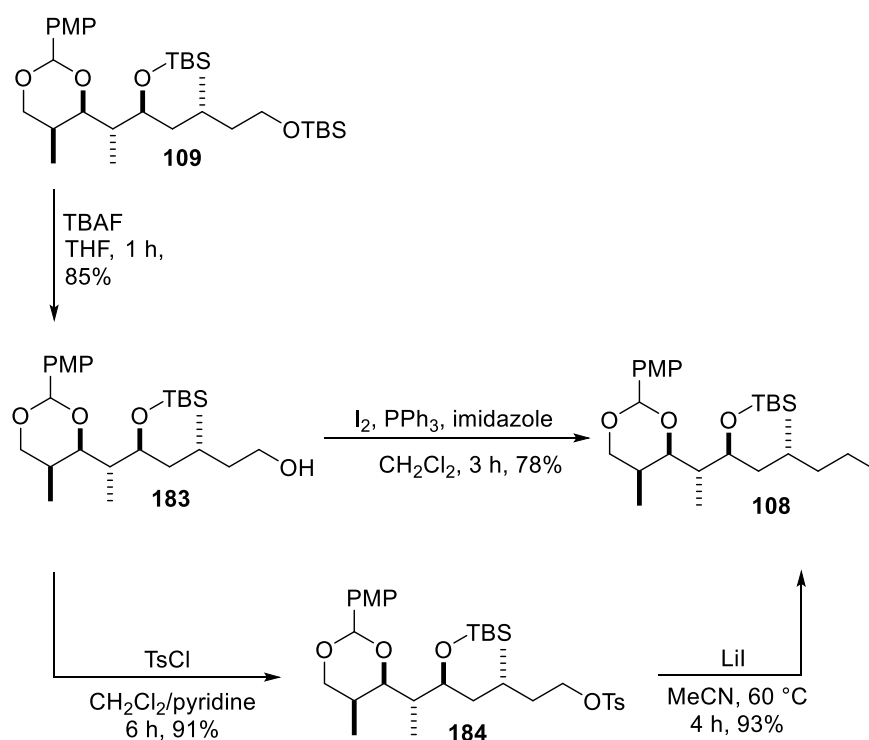
Scheme 46: Use of a Suzuki coupling in Marshall's Discodermolide synthesis

In order to trial this new approach, model iodide **173** was submitted to Marshall's conditions (although using Pd(PPh₃)₄ as the palladium source instead). In our hands, a side product **177** was observed (Scheme 44). Frustratingly, this was inseparable from alkene **176** by flash column chromatography. Despite extensive efforts to exclude moisture from the reaction, the high reactivity of the alkyl lithium species led to some proton abstraction before the anion could be trapped out as the boronate. Despite this, a 2.3:1 ratio of alkene **176** to alkane **177** in an 82% combined yield proved encouraging enough to pursue this route.

Although the halide displacement studies had proved unsuccessful, the promising results from the Suzuki coupling provided confidence in an alkyl iodide providing a useful functional handle from which to form the C₂-C₃ bond. Attention therefore turned to the conversion of silyl ether **109** into iodide **108** (Scheme 47). Primary silyl ether **109** was selectively deprotected under standard conditions with TBAF in good yield (85%). Again, careful monitoring by TLC and portionwise addition of TBAF allowed for the

minimum of *bis*-deprotection, with some starting material recovered in most cases.

Conversion of the resultant primary alcohol to the corresponding iodide was explored *via* two routes. Appel conditions (I_2 , PPh_3 , imidazole) delivered the product cleanly, but consistently in 75-80% yield. A two-step procedure was therefore attempted. Treatment of primary alcohol **183** with tosyl chloride in CH_2Cl_2 and pyridine afforded tosylate **184** in 91% yield, which was then displaced with lithium iodide at 60 °C furnishing the desired iodide in 93% yield. This two-step procedure therefore provided a small improvement in the overall yield (85%).



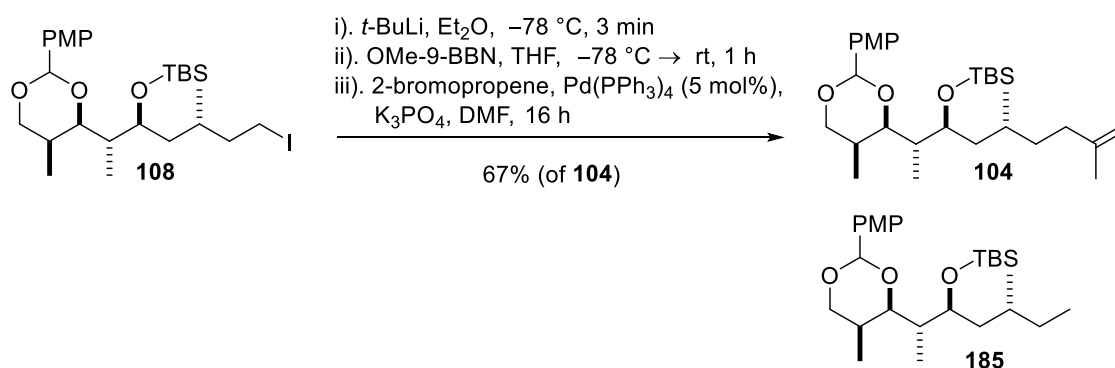
Scheme 47: Conversion of silyl ether **109** to iodide **108**

With iodide **108** in hand, Marshall's conditions could be employed to form the C_2 - C_3 bond. A similar result was obtained to that observed with the model system. The product ratio between alkene **104** and side product alkane **185** was always between 1.5:1 and 3:1 in favour of the desired alkene, generally improving with increased scale. As well as the $Pd(PPh_3)_4$ catalyst used in the model studies, $Pd(dppf)Cl_2$ (as used by Marshall) was trialed although results were comparable (**Table 8**, entries **1** and **5**)

A significant improvement in the product ratio of the Suzuki coupling was observed when a new bottle of *t*-BuLi was used (**entry 6**), indicating the noteworthy influence of reagent quality on the reaction.

Ultimately, the best results were obtained on larger scales (320 mg and 400 mg), when product ratios between alkene **104** and alkane **185** around 3:1 were reliably observed).

A palladium-catalysed Negishi coupling, replacing the OMe-9-BBN with freshly dried zinc (II) chloride, was also attempted (**entry 7**). Whereas the Suzuki coupling necessitated the addition of the OMe-9-BBN subsequent to that of the *t*-BuLi, it was hoped that pre-mixing of the alkyl iodide and zinc (II) chloride prior to *t*-BuLi addition would improve the alkene:side product ratio. Disappointingly, transmetallation to the appropriate organozinc species appeared to be ineffective and only side product **185** was isolated.



Scheme 48: Construction of C₂-C₃ bond via a lithiation, borylation, Suzuki coupling sequence

Entry	Scale	Pd Source	Product ratio 104:185	Overall yield
1	45 mg	Pd(PPh ₃) ₄	1.6:1	76%
2	100 mg	Pd(PPh ₃) ₄	1.9:1	72%
3	80 mg	Pd(PPh ₃) ₄	1.4:1	78%
4	130 mg	Pd(PPh ₃) ₄	2.3:1	84%
5	50 mg	PdCl ₂ (dppf) ^a	1.8:1	69%
6 ^b	50 mg	PdCl ₂ (dppf) ^a	3.0:1	76%
7 ^c	30 mg	Pd(PPh ₃) ₄	0:1	60%
8	320 mg	PdCl ₂ (dppf) ^a	2.9:1	83%
9	400 mg	PdCl ₂ (dppf) ^a	3.0:1	87%

a: 7.5% catalyst loading used with PdCl₂(dppf)

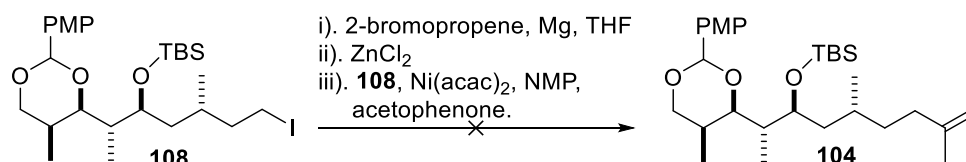
b: New bottle of *t*-BuLi used

c: ZnCl₂ used instead of OMe-9-BBN

Table 8: Attempted optimisation of C₂-C₃ bond formation via an in-situ Suzuki coupling

In pursuit of obtaining a higher yield and minimising the production of unwanted side products, a nickel-catalysed Negishi coupling using conditions developed by Knochel was trialled.⁹⁹ Grignard formation from 2-bromopropene was followed by transmetalation to the corresponding organozinc species. Knochel discovered that the use of electron-poor aryl additives, such as acetophenone, promoted the cross coupling of diorganozinc species with primary alkyl iodides, by binding to nickel and promoting reductive elimination.

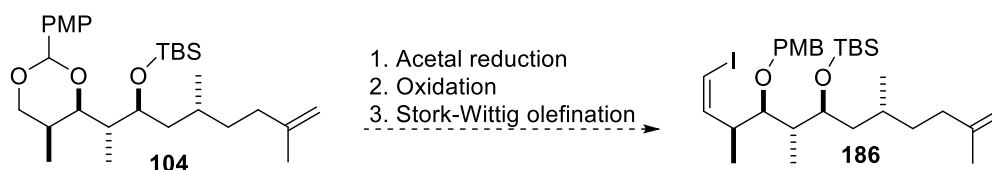
By avoiding the high-energy alkyl lithium species required in the previous methodology, it was hoped that formation of the proto-deiodinated product **185** would be reduced. Disappointingly though, the reaction was not successful and only starting material was recovered (**Scheme 49**). With the lithiation/borylation/Suzuki coupling procedure providing sufficient material throughput for fragment completion, attempts to further optimise this step were not carried out.



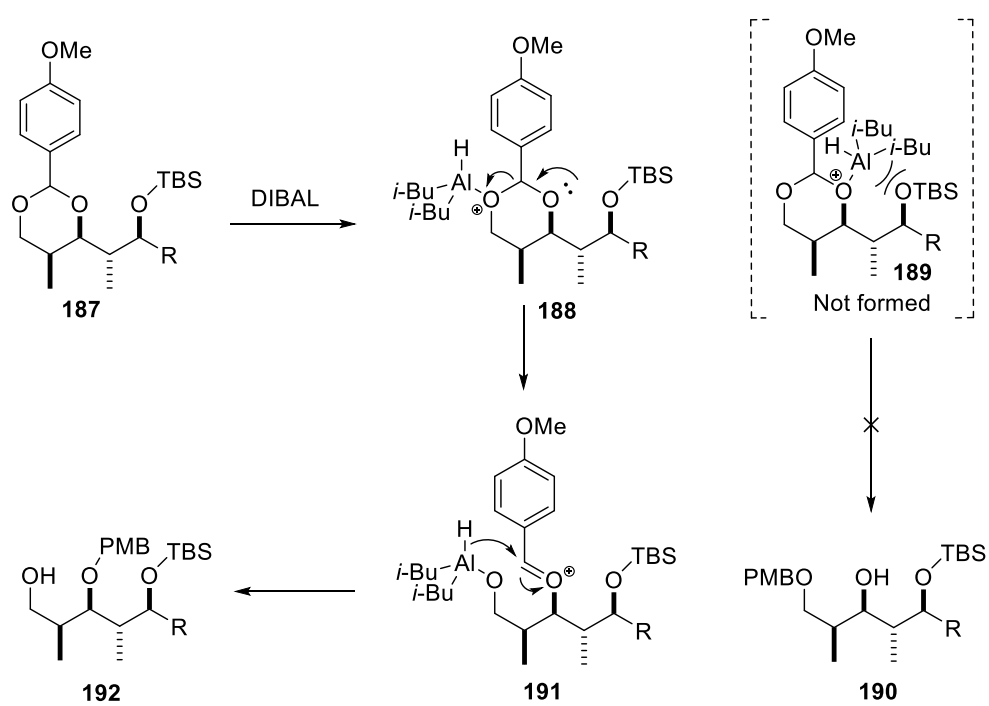
Scheme 49: Attempted nickel-catalysed Negishi coupling

2.3.4 Elaboration of C₁₂ Terminus

With a view to constructing a truncated analogue of the C₁-C₁₂ fragment for coupling studies (and also providing material to investigate a late stage regio- and stereoselective dihydroxylation strategy), studies were carried out to elaborate the C₁₂ terminus at this junction. It was envisaged that a regioselective reduction of acetal **104** should give the primary alcohol, which could then be oxidised to the corresponding aldehyde. From this aldehyde, a Stork-Wittig olefination should provide (Z)-vinyl iodide **186** (**Scheme 50**). Alternatively, the aldehyde could be converted into the terminal alkyne (*via* a Seyferth-Gilbert homologation), providing flexibility in the fragment coupling approach.



*Scheme 50: Proposed route to truncated analogue **186***

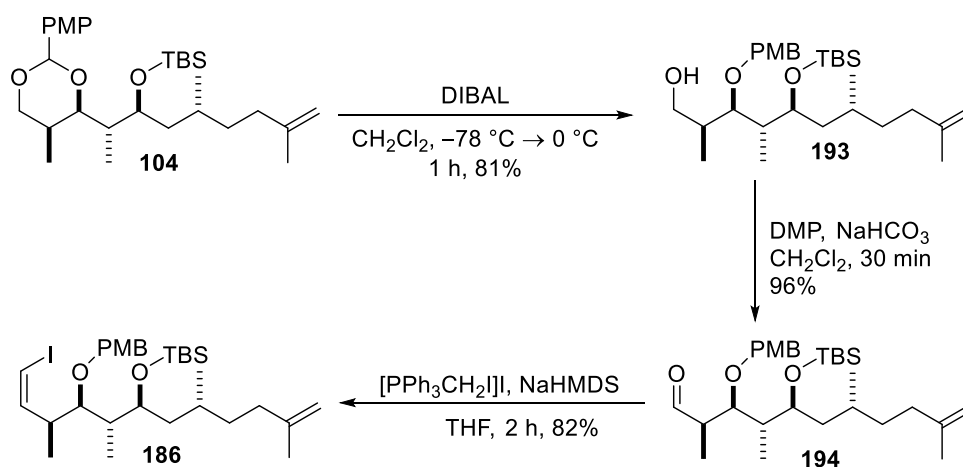


Scheme 51: Regioselective PMP acetal reduction to give the more substituted PMB ether **192**

PMP acetal **104** was treated with DIBAL at $-78\text{ }^{\circ}\text{C}$ before slowly warming to $0\text{ }^{\circ}\text{C}$ to afford the secondary PMB ether **193** in 81% yield.

DIBAL coordinates selectively to the less hindered side of the PMP acetal, effecting opening of the acetal to give oxonium species **191** and subsequent internal hydride delivery, placing the PMB ether on the more hindered secondary alcohol. The steric clash between the bulky *iso*-butyl groups on the aluminium and the congested C_7 and C_8 centres led to the product (**190**) from intermediate **189** not being observed (**Scheme 51**).

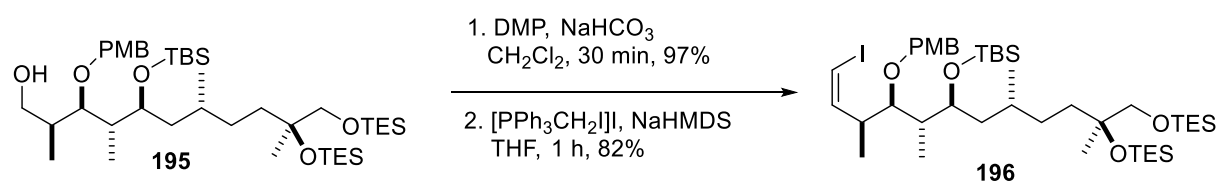
Oxidation of the primary alcohol under Swern conditions (oxalyl chloride, DMSO, triethylamine) disappointingly delivered the product (**194**) in only 70% yield. A switch to Dess-Martin periodinane however, afforded this transformation in an excellent 96% yield. (*Z*)-vinyl iodide **186** was then installed from aldehyde **194** making use of the Stork-Zhao reagent ($[\text{PPh}_3\text{CH}_2\text{I}]\text{I}$) and NaHMDS as a base. Initial attempts with 1.5 equivalents of both the Wittig salt and base led to incomplete reaction (~50% conversion), but increasing this to 3.5 and 3.0 equivalents respectively pushed the reaction to completion, giving the product in a satisfactory 82% yield (**Scheme 52**).



*Scheme 52: Elaboration of C_{12} terminus into (*Z*)-vinyl iodide **186***

2.3.5 Sharpless Dihydroxylation and Completion of the Fully Elaborated C_1 - C_{12} Fragment

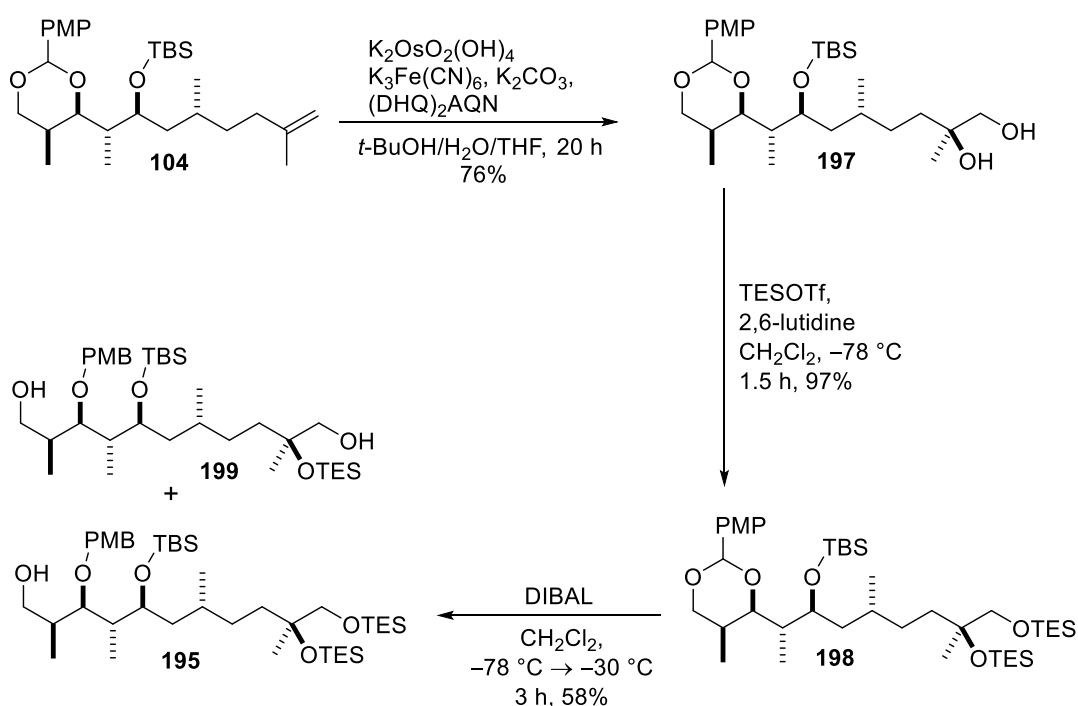
Synthesis of the full C_1 - C_{12} fragment, however, requires oxygenation at the C_1 and C_2 positions. Previous investigations (as described in section 2.2.1) showed the suitability of this alkene for Sharpless asymmetric dihydroxylation as a method to install the requisite diol. The previous ligand screen had highlighted $(\text{DHQ})_2\text{AQN}$ as the optimum ligand. Transferring these conditions to alkene **104** pleasingly



Scheme 53: Completion of the fully elaborated C₁-C₁₂ fragment

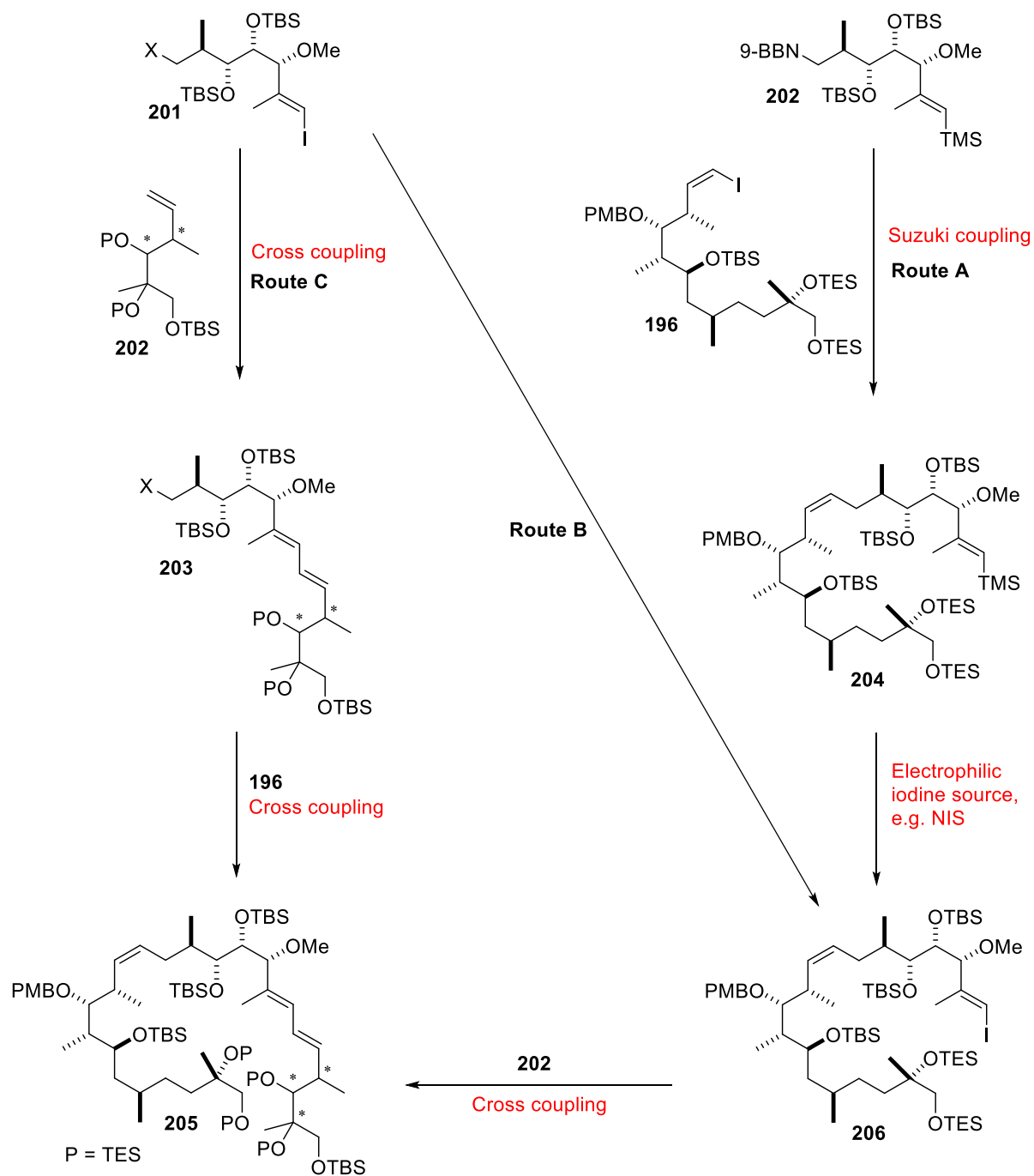
appeared to give the diol **197** as a single product (**Scheme 54**). At this stage in the synthesis, separation of the diol from side product **185** is possible. *Bis*-TES protection of the diol with TESOTf and 2,6-lutidine then gave silyl ether **198** in an excellent 97% yield. The Lewis acidic nature of the TESOTf also served to equilibrate the PMP acetal to a single diastereomer. Coordination of the Lewis acid to one of the acetal oxygens promotes ring opening to give an oxonium species, which can then be reattacked by the free alcohol reforming the PMP acetal.

The PMP acetal **198** was then opened to give primary alcohol **195**. Unfortunately, under the same conditions as used previously (addition of DIBAL at $-78\text{ }^{\circ}\text{C}$ followed by warming to $0\text{ }^{\circ}\text{C}$), significant primary TES deprotection was observed giving a 1:1 product ratio between **195** and **199**. With no obvious method to distinguish between the two primary alcohols in the side product, eliminating its production was highly desirable. Careful monitoring of the reaction by TLC showed no discernible acetal opening below $-35\text{ }^{\circ}\text{C}$, but little TES deprotection was observed below $-25\text{ }^{\circ}\text{C}$, providing a useful, but tight window. An optimum reaction temperature of $-30\text{ }^{\circ}\text{C}$ was therefore identified and the product was isolated in 58% yield.



*Scheme 54: Elaboration of alkene **104** to alcohol **195***

Oxidation of primary alcohol **195**, under Dess-Martin conditions, gave the resultant aldehyde (**200**) in 97% yield, which was subsequently subject to a Stork-Zhao olefination, as described previously, providing the vinyl iodide **196** in 82% yield (**Scheme 53**). This completed the synthesis of the fully-elaborated $\text{C}_1\text{-C}_{12}$ fragment in 4.5% yield over 17 steps.



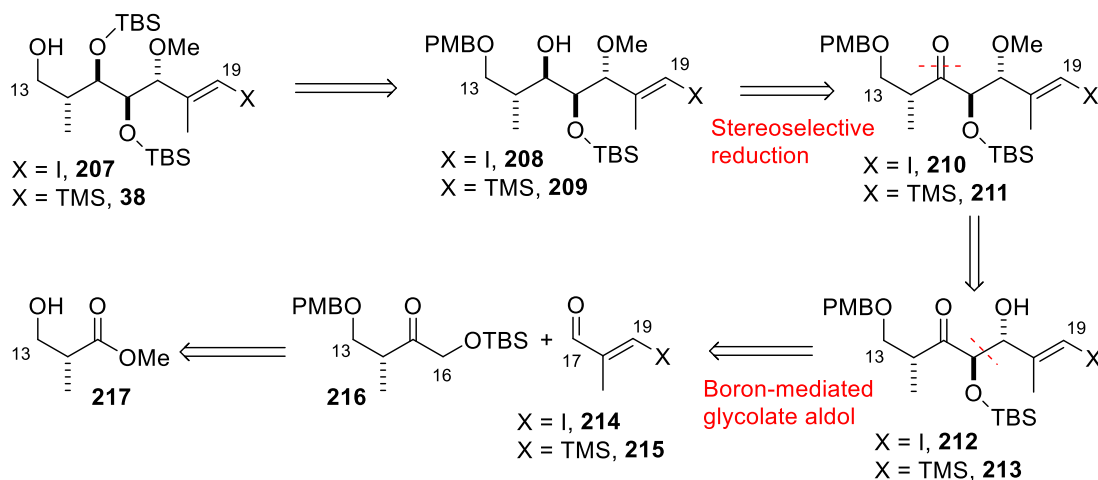
Scheme 55: Fragment union options originating from vinyl silane **202** or vinyl iodide **201**

Chapter 3: Results and Discussion – Part II

Synthesis of the C₁₃-C₁₉ Vinyl Iodide

Some of the work described in the chapter was carried out by T Balan.¹⁰⁰ For clarity and completeness some of his results are also included below. Unless otherwise stated however, all reactions were performed by the author and all stated yields are those obtained by the author.

3.1 Retrosynthesis



Scheme 56: Retrosynthetic analysis for the C₁₃-C₁₉ fragment

In attempting to leave as much flexibility in the fragment union strategy as possible, two functional groups at the C₁₉ position were proposed, specifically a vinyl iodide and a vinyl silane. It was envisaged that the latter could act as a 'protecting group' for the iodide, facilitating C₁₂-C₁₃ bond formation *via* a palladium catalysed cross coupling, prior to revealing the vinyl iodide with an electrophilic iodine source^{101,102} and subsequent C₁₉-C₂₀ bond construction (**Scheme 55, route A**). Alternatively, a fragment union strategy originating from the C₁₈-C₁₉ vinyl iodide could proceed *via* either of two possible routes. Initial construction of the C₁₂-C₁₃ bond in a non-metal catalysed reaction (which should be compatible with the vinyl iodide) would give intermediate **206**. This could then undergo a cross coupling with the C₂₀-C₂₅ fragment to give the complete C₁-C₂₅ piece (**route B**). Otherwise, the cross coupling to construct the C₁₉-C₂₀ bond could take place first, giving intermediate **203**. With the vinyl iodide no longer in place, a palladium catalysed cross coupling could then be used to afford the fragment union with the C₁-C₁₂ piece (**route C**).

We imagine that the C₁₄-C₁₇ stereotetrad could be constructed from two stereocontrolling reactions; namely a boron mediated *anti*-glycolate aldol and a stereoselective reduction of the C₁₅ ketone (**Scheme 56**). Felkin control should hopefully install the latter with high diastereoselectivity.

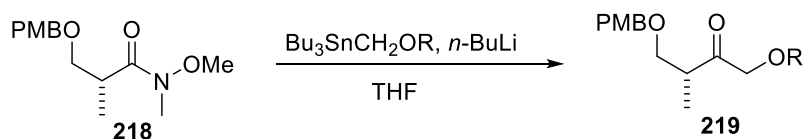
Although this C₁₅/C₁₇ 1,3-*anti* stereochemistry could also be generated *via* an Evan-Saksena^{103,104} or Evans-Tischenko¹⁰⁵ reduction, the methylation required at C₁₇ and thus the orthogonality of protecting groups required leads this to be a less desirable route. Our proposed strategy involving direct methylation of the aldol adduct followed by a Felkin controlled reduction should afford alcohol **208/209** in only three steps from ketone **216**. The glycolate aldol is well preceded on similar α -hydroxy ketones, based on investigations into solid-supported aldol reactions by Paterson.¹⁰⁶ The aldol precursor **216**, could arise from the appropriate methyl ketone, derived from Roche ester in three steps.

3.2 Synthesis of Aldol Adducts 212 and 213

3.2.1 Optimisation of the α -Hydroxylation of Methyl Ketone 220

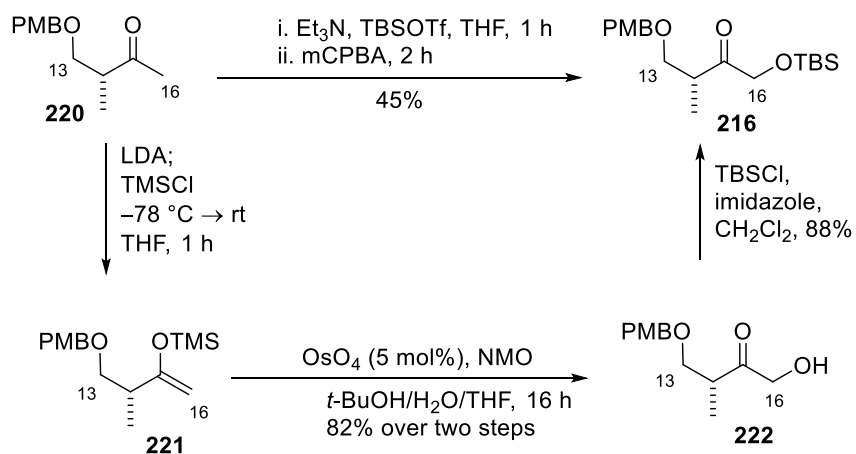
Note: Much of the chemistry in this fragment was explored in the enantiomeric series, using (R)-Roche ester as the corresponding starting material, due to its greater availability within our laboratory. Results where the chemistry was only carried out in this enantiomeric series will be noted accordingly.

Previously in the Paterson group, α -alkoxy ketones derived from Roche ester had been constructed from the appropriate Weinreb amide (**218**) and organotin reagent shown in **Scheme 57**.^{107,108} Unfortunately, this methodology has been shown to be incompatible with silyl protecting groups. In order to keep the endgame as concise as possible a silyl protecting group at this position is highly desirable. The use of toxic organotin reagents on large scale is also non-ideal.



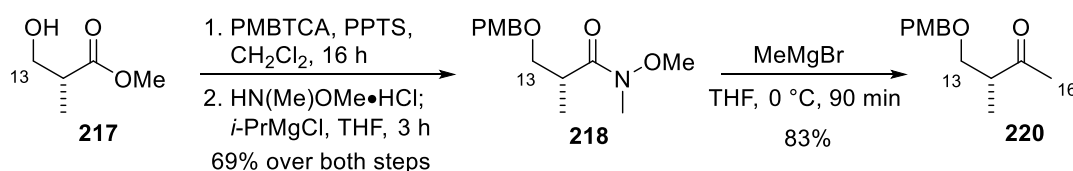
Scheme 57: Previous methodology used to construct alkoxy ketones derived from Roche ester

Balan sought to investigate alternative methodology for the formation of such α -alkoxy ketones. A Rubottom-type oxidation was proposed, forming the silyl enol ether *in situ* before treatment with mCPBA. Rearrangement of the ensuing epoxide with silyl migration affords the protected hydroxy ketone. Typically, the silyl migration is incomplete, so a mixture of the protected (**216**) and unprotected (**222**) alcohols is recovered, which can be converted to a single product by subsequent treatment with TBSCl and imidazole.



*Scheme 58: Rubottom and Upjohn oxidations to afford α -alkoxy ketone **216***

Synthesis of methyl ketone precursor (**220**) began from (*S*)-Roche ester *via* the same methodology as described in **section 2.3.1**. Protection of the primary alcohol as the PMB ether under mild conditions (PMBTCA, PPTS), followed by reaction with (*N,O*)-dimethylhydroxylamine hydrochloride in the presence of isopropyl magnesium chloride, delivered Weinreb amide (**218**) in 69% yield over both steps. Treatment with methyl magnesium bromide then furnished methyl ketone **220** in 83% yield (**Scheme 59**).

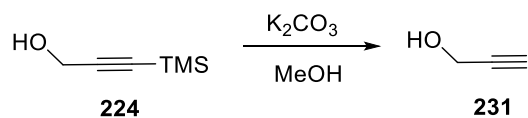


Scheme 59: Synthesis of methyl ketone 220

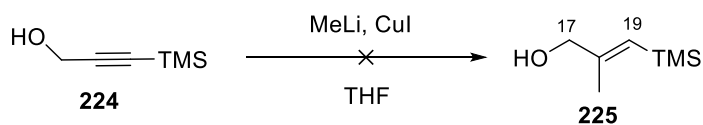
Disappointingly, yields for the Rubottom oxidation were consistently low (40-45%), with significant amounts of starting material recovered (**Scheme 58**). Whilst this could be recycled to improve the overall conversion, it was deemed an inelegant solution to the problem. It was surmised that the acidic nature of the mCPBA (especially considering the presence of the corresponding carboxylic acid found in the commercially available product), was somewhat incompatible with the silyl enol ether.

An alternative oxidation strategy was therefore sought. Unpublished investigations into the synthesis of spirastrellolide by Paterson made use of an Upjohn dihydroxylation of a silyl enol ether to furnish the same α -hydroxy ketone intermediate.¹⁰⁹ Whereas the silyl migration in the previous route necessitated the use of a TBS enol ether to produce the desired TBS protected alcohol, in this case any silyl electrophile could be utilised in forming the silyl enol ether, so TMSCl provided an inexpensive alternative.

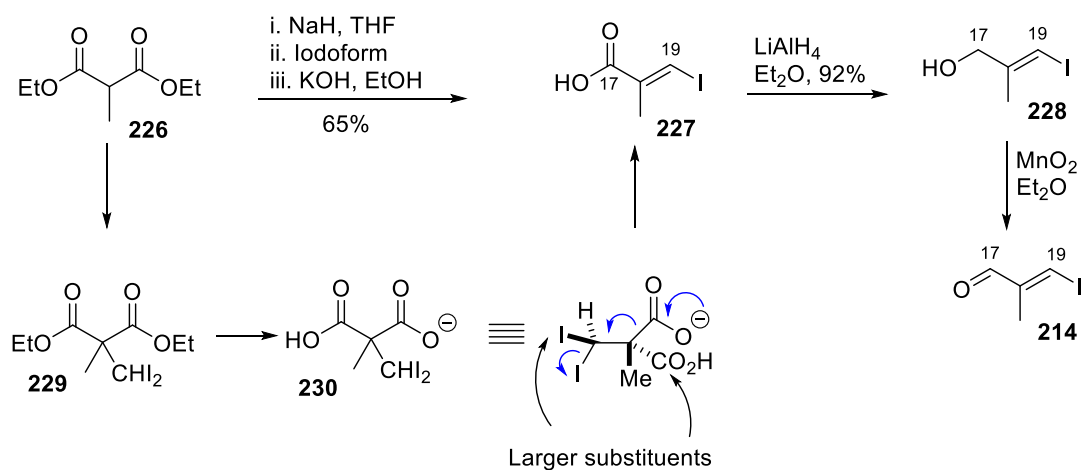
Silyl enol ether **221** was therefore produced using LDA and TMSCl at -78 °C. A relatively high osmium loading of 5 mol% was required for the dihydroxylation to reach completion. Pleasingly though, this transformation delivered alcohol **222** in 82% yield. The primary alcohol then underwent silyl protection with TBSCl and imidazole to afford the α -silyloxy ketone **216** in 88% yield, providing a far more satisfactory route to this aldol precursor.



*Scheme 3: Selective deprotection of alkynyl silane **224** with K₂CO₃ and MeOH*



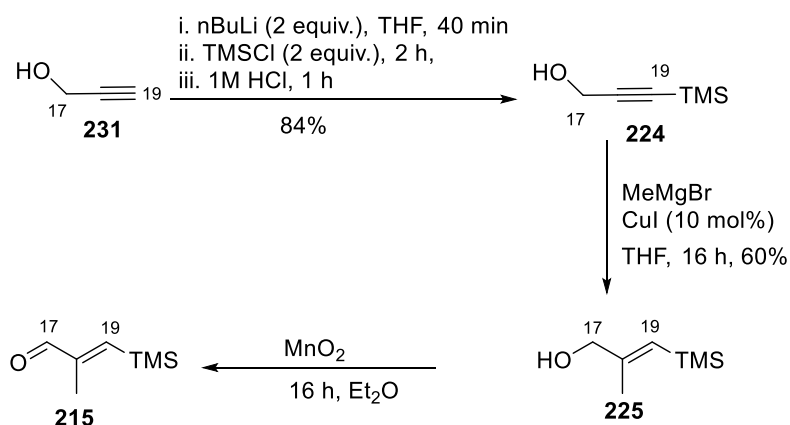
*Scheme 61: Attempted carbocupration of alkyne **224** with a Gilman reagent*



*Scheme 62: Synthesis of aldehyde **214***

3.2.2 Synthesis of Vinyl Silane **215**

The synthesis of vinyl silane **215** proved more challenging than anticipated. Propargyl alcohol was doubly-deprotonated with *n*-BuLi and the ensuing dianion *bis*-silylated with TMSCl. An acidic work up then selectively deprotected the silyl ether, giving TMS alkyne **224** in 84% yield. The copper-catalysed carbomagnesiation of the same alkyne has been reported in the literature by Spino and coworkers,¹¹⁰ giving the resulting vinyl silane in 93% yield after silyl protection of the alcohol. Disappointingly in our hands, although the reaction proceeded very cleanly, it was prone to stalling and at best a 60% conversion was observed (**Scheme 63**). Balan reported a variation in conversions based on the batch of the copper (I) iodide used. Unfortunately, the starting material and proved inseparable by TLC. Although some separation was possible after deprotection of the remaining alkynyl silane with potassium carbonate in methanol (**Scheme 60**), this was an inelegant solution. The attempted use of a pre-formed Gilman reagent (between MeLi and CuI)¹¹¹ also proved ineffective, only returning starting material (**Scheme 61**).



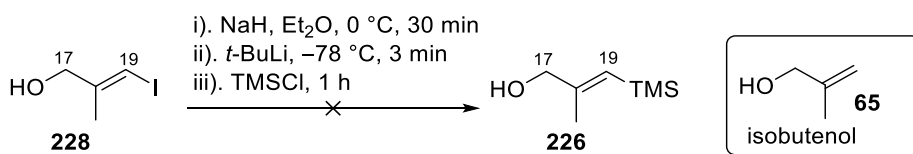
Scheme 63: Synthesis of vinyl silane **215**

3.2.3 Revised Strategy and Synthesis of Vinyl Iodide **214**

Synthesis of the corresponding vinyl iodide **214** fortunately proved less challenging and began with diethyl methylmalonate following a known literature procedure by Baker and coworkers (**Scheme 62**).¹¹² Deprotonation with sodium hydride and subsequent trapping with iodoform gave intermediate **229**. Hydrolysis of the *bis*-ester with potassium hydroxide generated *bis*-acid **230** which could then undergo an E2 elimination to give vinyl iodide **227**. Placement of the two larger groups *anti* to each other, during the elimination, selectively gives the (*E*)-vinyl iodide. Reduction of the resultant carboxylic acid with lithium aluminium hydride proceeded smoothly to give allylic alcohol **228**. This was subsequently oxidised to aldehyde **214** with manganese dioxide, the reaction mixture filtered and excess solvent

removed carefully *in vacuo* to give a concentrated solution of the aldehyde in Et₂O, which could then be dried over CaH₂ and cannulated directly into the glycolate aldol reaction without further purification.

Attempts were also made to convert vinyl iodide **214** to vinyl silane **215** via a lithium-halogen exchange, followed by subsequent trapping with TMSCl (**Scheme 64**). Regrettably, even with the prior addition of sodium hydride to deprotonate the primary alcohol, significant amounts of the isobutenol side product were observed, so this alternative synthesis was not pursued.



*Scheme 64: Attempted conversion of vinyl iodide **228** into vinyl silane **226***

3.2.4 Glycolate Boron Aldol

With ketone **220** and both aldehydes **214** and **215** in hand, the boron-mediated glycolate aldol could be attempted. Enolisation of α -silyloxy ketone **220** with dicyclohexylboron chloride and triethylamine selectively gave the (*E*)-enolate, via a similar proposed transition state (**TS-232**) to that described in **section 2.3.1**. A favourable H-bonding interaction between one of the α -protons and the chloride, and the preference for the bulky silyl ether to sit *trans* to the carbonyl dictates the selectivity for enolate geometry (**Figure 23**).

Again, a boat transition state (**TS-233**) is proposed for the aldol reaction, with a formyl hydrogen bond between the PMB ether lone pair and aldehydic proton stabilising the transition state and allylic strain minimised by placing the C₁₄ methyl out of the transition state and the corresponding proton eclipsing the double bond.

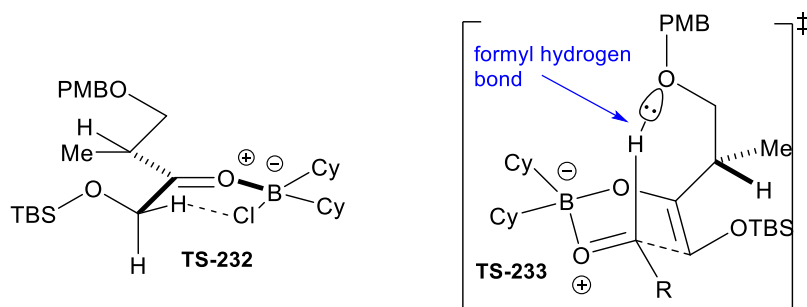
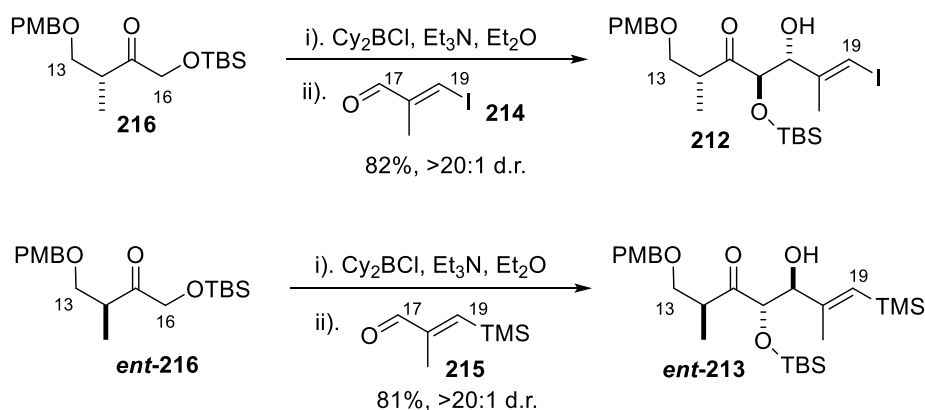


Figure 23: Proposed transition states for enolate formation and glycolate aldol

Pleasingly the reaction proceeded smoothly in both cases with the vinyl silane and vinyl iodide- bearing aldehydes producing aldol adducts **ent-213** and **212** in 81% and 82% yields respectively (both in >20:1 d.r.), following an oxidative work up with hydrogen peroxide and pH 7 buffer (**Scheme 65**). The excess of aldehyde used did appear to have an influence on the yield, with that for adduct **ent-213** dropping to 56% when only 3 equiv. of aldehyde **215** was used. Raising this to 4.5 equiv. increased the yield to 81%.

Mosher ester analysis⁹⁷ was carried out on vinyl iodide aldol adduct **235** by Balan, confirming the absolute stereochemistry of the newly-formed alcohol.¹⁰⁰

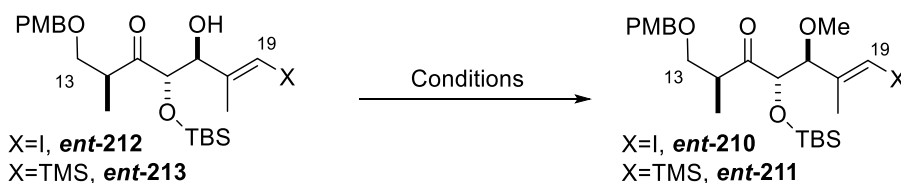


Scheme 65: Boron-mediated glycolate aldol reactions

3.3 Completion of the C₁₃-C₁₉ Fragment

3.3.1 Studies into C₁₇ Methylation

With both aldol adducts in hand, attention turned to the methylation of the C₁₇ alcohol (**Scheme 66**). Whilst this alcohol could be protected and methylated at a later stage of the synthesis, direct methylation of the aldol represented the most attractive option. Balan focussed on investigating this transformation on the vinyl silane bearing aldol adduct, with the author repeating several experiments to confirm the results as well as exploring the vinyl iodide series.



*Scheme 66: Attempted methylation of aldol adducts **ent-212** and **ent-213***

Reacting the vinyl silane with Meerwein's salt (Me_3OBF_4) in the presence of either Proton-sponge® or 2,6-ditertbutyl pyridine (**Table 9, entries 1 and 2**) led to a mixture of three products being formed. Unfortunately, when the methylating reagent was changed to methyl triflate, no reaction was observed at room temperature. Moreover, the same epimerisation result was observed when the reaction was carried out at 40 °C. Only starting material was recovered with iodomethane and silver (I) oxide.

With the vinyl silane proving incompatible with all the conditions attempted, attention turned to the vinyl iodide. Disappointingly, treatment with sodium hydride and iodomethane (**entry 6**) led to the isolation of ketone **220**, attributable to a retro-aldol process. Employment of Meerwein's salt and Proton-sponge® at 0 °C resulted in only the recovery of starting material, but gratifyingly when the reaction was carried out at room temperature the desired product could be isolated in 82% yield. Despite large excesses of both reagents being used (8 and 10 equivalents of Meerweins's salt and Proton-sponge® respectively), the reaction could only be pushed to completion on small scale. Allowing the reaction to continue for 16 hours didn't appear to lead to any appreciable degradation of the product and afforded a slightly higher conversion rate. Yields based on recovered starting material were typically greater than 90%, facilitating the recycling of unreacted material.

Entry	X = ?	Methylating reagent	Base	Temperature	Result
1	TMS	Me_3OBF_4	Proton-sponge®	0 °C	Mixture
2 ^a	TMS	Me_3OBF_4	2,6-ditertbutyl pyridine	0 °C	Mixture
3 ^a	TMS	MeOTf	2,6-ditertbutyl pyridine	rt	No reaction
4 ^a	TMS	MeOTf	2,6-ditertbutyl pyridine	reflux at 40 °C	Mixture
5	TMS	MeI	Ag_2O	0 °C	No reaction
6	I	MeI	NaH	rt	Retrol-aldol
7	I	Me_3OBF_4	Proton-sponge®	0 °C	No reaction
8	I	Me_3OBF_4	Proton-sponge®	rt	82%

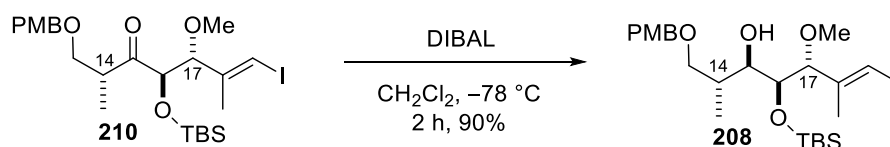
a: Result obtained by T Balan

Table 9: Conditions for C_{17} methylation of aldol adducts ent-212 and ent-213

With no promising methylation results in the vinyl silane series and recognition of the difficulties in preparing aldehyde **215**, it was concluded that the silane was no longer a viable functional group to use in the synthesis. Whilst there were attractive features of the approach, in relation to the later fragment union strategy, it became apparent that it was not sufficiently compatible with the earlier chemistry required in the fragment synthesis. Therefore the synthesis was progressed from this point forward solely in the vinyl iodide series.

3.3.2 Studies into Stereoselective C₁₅ Reduction

As outlined previously, it was envisaged that the C₁₅ stereocentre could be formed *via* the substrate-controlled reduction of ketone **210** (Scheme 67). Three possible transition state models were considered for this transformation, namely the Felkin-Ahn, polar Felkin-Ahn or Evan polar models. These take the influence of each of the neighbouring C₁₄, C₁₆ and C₁₇ stereocentres into consideration.



Scheme 67: Stereoselective reduction of ketone **210** with DIBAL

In the Felkin-Ahn model¹¹³ (Figure 24), the two lowest energy conformers are defined as those where the largest group (in this case, CH₂OPMB) is placed perpendicular to the carbonyl. The dipoles of the PMB ether and carbonyl are also opposed. In the more reactive of these conformers, the nucleophile can attack at the Bürgi-Dunitz angle (107 °) on the side of the smallest group (H), giving the Felkin product, in which the C₁₄ methyl and C₁₅ alcohol are *anti*. The less reactive conformer experiences unfavourable steric interactions between the C₁₄ methyl group and the incoming nucleophile.

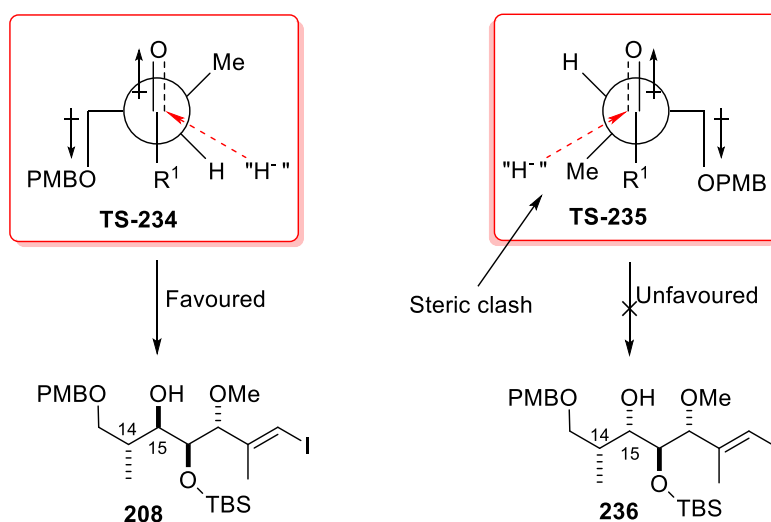


Figure 24: Analysis of the Felkin-Ahn model for the reduction of the C₁₅ ketone

The polar Felkin-Ahn model takes into consideration the effect of the C₁₆ stereocentre (**Figure 25**). In this model, the most polar group α to the carbonyl is considered to be the largest. This can be attributed to the favourable overlap between the $\sigma^*_{\text{C-OTBS}}$ and the $\pi^*_{\text{C=O}}$, increasing the carbonyl reactivity. Attack of the nucleophile, again at the Bürgi-Dunitz angle on the side of the hydrogen, leads to the same Felkin product as in **Figure 24**.

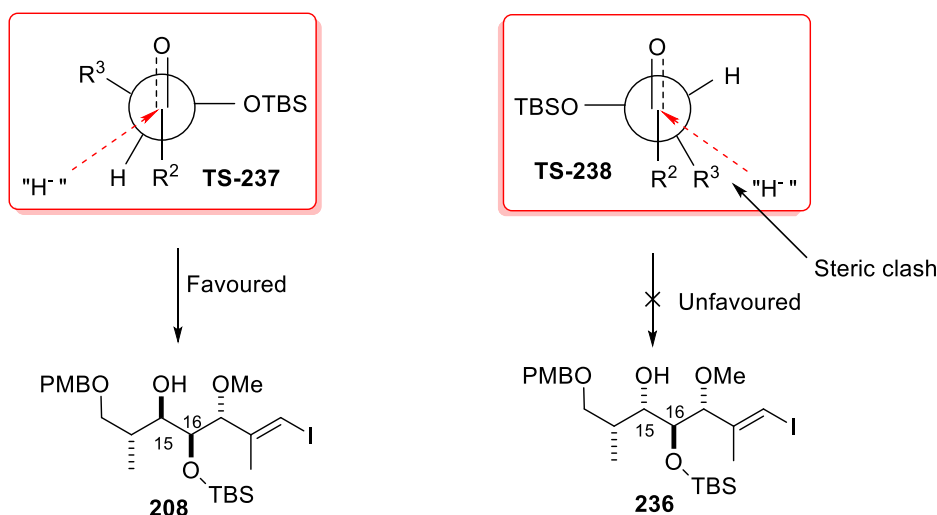


Figure 25: Analysis of the polar Felkin-Ahn model for the reduction of the C₁₅ ketone

The other possible model which could be considered is the Evans' polar model,¹¹⁴ which would take into account the stereochemistry at the C₁₇ position to influence the stereoselectivity of the reduction (**Figure 26**). Again, the largest group is placed perpendicular to the carbonyl with the carbonyl and methoxy dipoles opposed. Attack of the nucleophile over the smallest group in this instance would lead to the anti-Felkin product. However, we postulated that this transition state would be high in energy due to steric clashing between the bulky silyl protecting group and the carbonyl.

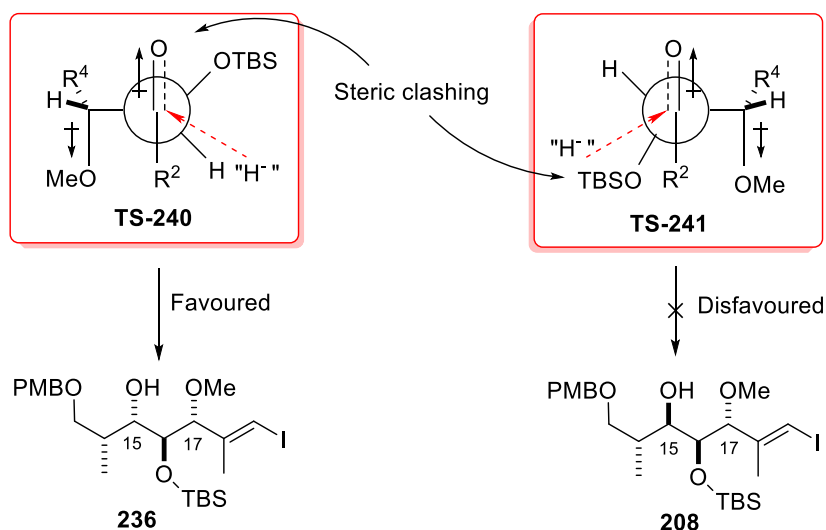


Figure 26: Analysis of the Evans polar model for the reduction of the C₁₅ ketone

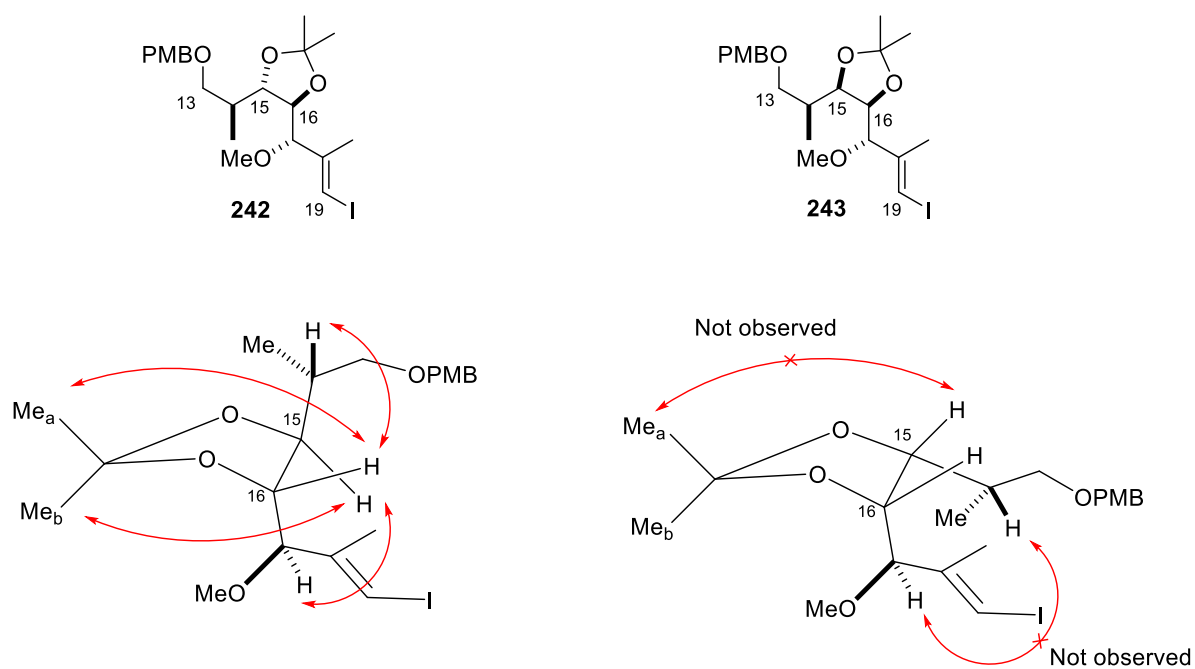
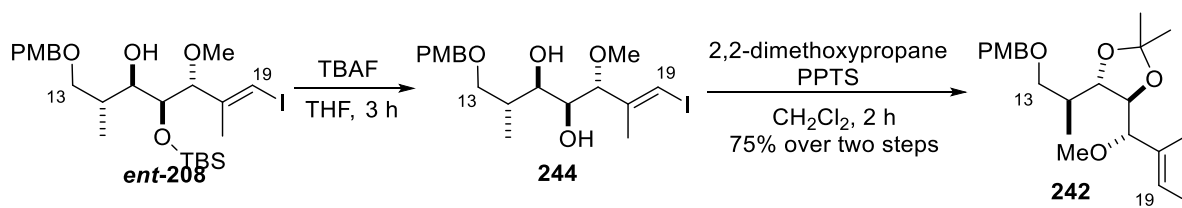


Figure 27: Key NOE interactions used to determine the C₁₅ stereochemistry

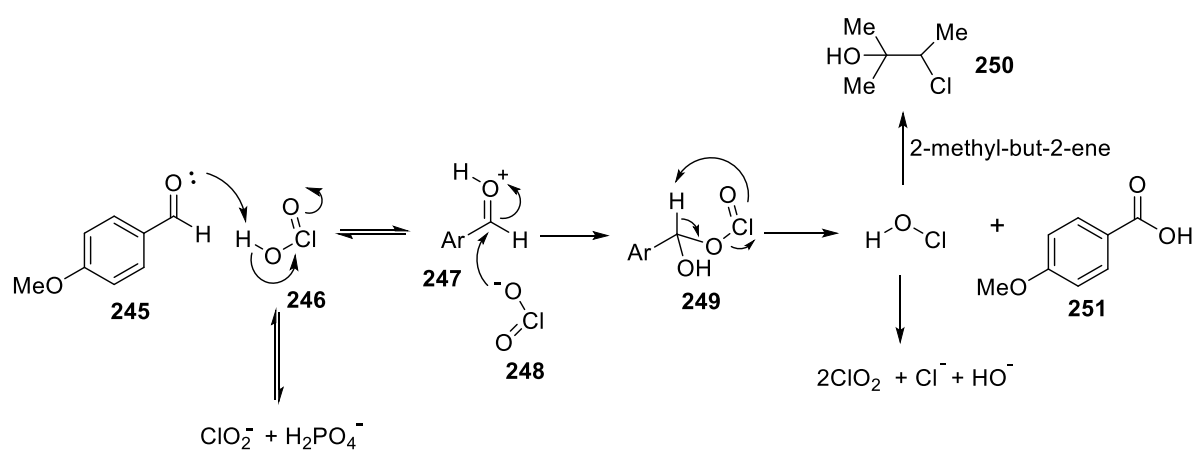
Analysis of these three models gave us sufficient confidence that substrate control should provide the required selectivity. Reduction with DIBAL at $-78\text{ }^{\circ}\text{C}$ led to a single product diastereomer being isolated. Attempts at forming the C_{15} Mosher esters to identify the configuration of the newly formed alcohol unfortunately proved unsuccessful. We postulated this was hampered by the considerable steric bulk of the surrounding stereogenic centres. The stereochemistry at C_{15} was instead confirmed by NOE studies on acetonide **242**. We proposed that formation of a five-membered ring would introduce a degree of rigidity to the molecule, allowing NOE interactions to confirm the unknown stereochemistry. J -based coupling constant analysis of both the linear and cyclic compounds was unlikely to elucidate the structure with any degree of confidence. Unlike six membered rings, five membered rings do not exhibit clear axial and equatorial proton environments.¹¹⁵ Silyl ether **208** was therefore deprotected with TBAF to reveal diol **244**, which was then protected as the corresponding acetonide, with 2,2-dimethoxypropane in the presence of PPTS (**Scheme 68**).



*Scheme 68: Formation of acetonide **242** for NOE studies to confirm C_{15} stereochemistry*

Analysis of a series of 1D NOEs was carried out to determine the acetonide stereochemistry. We hypothesised that in the *anti*-acetonide case, the C_{15} and C_{16} protons would exhibit asymmetric NOEs with respect to the two geminal methyl groups. A strong NOE was observed between the C_{16} proton and Me_a (combined with a weak NOE to Me_b), whereas the opposite was true for the C_{15} proton. In the *syn*-acetonide case, it was expected that both protons should observe similarly strong NOEs to one methyl group and correspondingly weak ones to the other.

We had envisaged that with the C_{15} and C_{16} protons diaxial, no NOE between them would be observed. Instead, an interaction was observed, originally assigned to a strong coupling effect providing an alternative pathway.¹¹⁵ A conformational search and reoptimisation of the lowest energy conformers with DFT (Geometries B3LYP/LANVCP**) however, provided the left-hand structure shown in **Figure 27**.¹¹⁶ With the C_{15} and C_{16} protons now both pseudoequatorial, this interaction is more logical. Importantly however, no NOE was observed between the C_{14} and C_{17} protons, providing good evidence for the left-hand structure opposite.



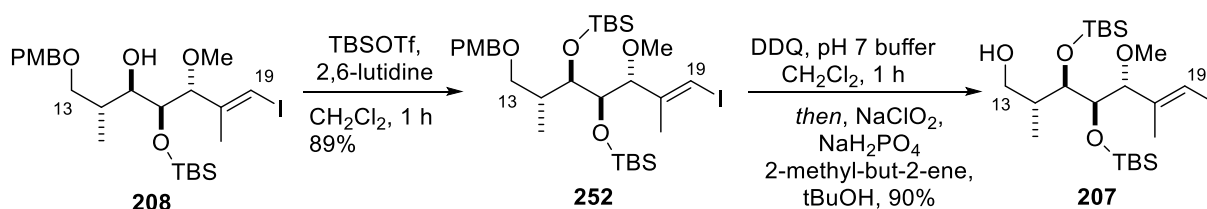
Scheme 69: Mechanism of the Pinnick oxidation

The high stereocontrol observed can be attributed to both the α -stereocentres directing the reduction from the same face, reinforcing the influence of each other.

Despite only a single equivalent of DIBAL being required in theory, the reaction suffered from incomplete conversion, necessitating the use of a greater reagent excess. Mostly starting material was returned upon the addition of 1.2 equiv. of DIBAL, but the reaction could be pushed to completion when this was increased to 5.0 equiv., affording the product in an excellent 90% yield.

3.3.3 Elaboration into the C₁₃ alcohol

The resultant alcohol (**208**), was silyl protected under standard conditions with TBSOTf and 2,6-lutidine, affording the TBS-ether (**252**) in 89% yield. The primary PMB ether was then deprotected with DDQ in the presence of pH 7 buffer (**Scheme 70**). The anisaldehyde by-product proved to be inseparable from alcohol **207**, so the crude mixture was subjected to Pinnick conditions to selectively oxidise the aldehyde to *p*-anisic acid. Protonation of the aldehyde by chlorous acid (generated *in situ* from sodium chlorite and sodium dihydrogen phosphate) promoted addition of the chlorate anion to provide intermediate **249**. Decomposition of this species delivered *p*-anisic acid (which could easily be removed with a basic wash). 2-methyl-but-2-ene was added to sequester out the hypochlorous acid, forming chlorohydrin **250**, preventing any unwanted side reactions (**Scheme 69**). Gratifyingly, this process provided the clean alcohol in 90% yield and the full fragment in 15% overall yield in 10 steps.



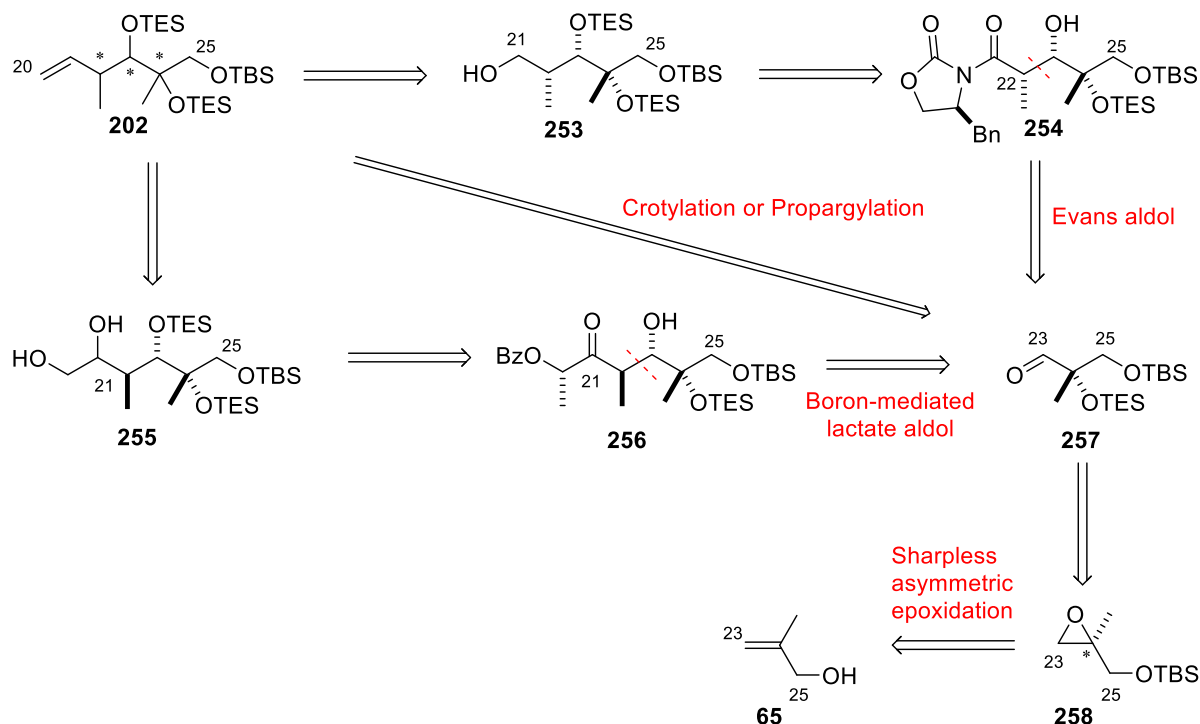
Scheme 70: Protection/deprotection to complete C₁₃-C₁₉ fragment

Chapter 4: Results and Discussion – Part III

Synthesis of the C₂₀-C₂₅ alkene

Some of the work described in the chapter was carried out by M Anketell. For clarity and completeness some of his results are also included below. Unless otherwise stated however, all reactions were performed by the author and all stated yields are those obtained by the author.

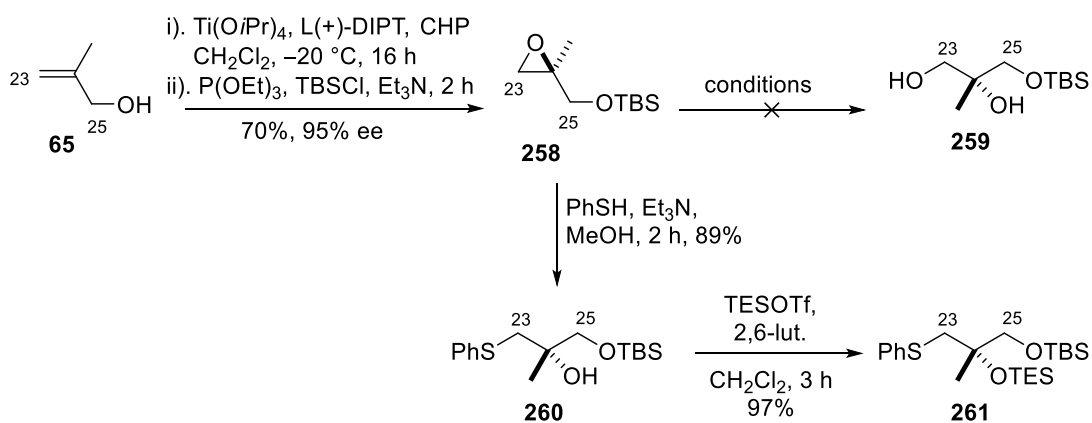
4.1 Retrosynthesis



Scheme 71: Retrosynthetic analysis for C₂₀-C₂₅ fragment

With all eight possible stereoisomers of the C₂₀-C₂₅ fragment requiring construction, it was of paramount importance that all three stereocentres could be installed *via* reagent control rather than substrate control (**Scheme 71**). Several different routes were considered including a potential crotylation or propargylation which would lead to alkene **202** from aldehyde **257**, following silyl protection (and reduction of the resultant alkyne in the propargylation case). Numerous methods for this can be found in the literature, which will be discussed in due course.

Alternatively, the *syn* stereochemistry across the C₂₂-C₂₃ bond could be installed *via* an Evans aldol,¹¹⁷ with subsequent auxiliary cleavage, oxidation and olefination. The corresponding *anti* diastereomer could be constructed utilising an aldol reaction of a lactate derived ketone,^{118,119} followed by auxiliary reduction, periodate cleavage and olefination.



*Scheme 72: Synthesis and attempted opening of epoxide **258***

Entry	Reagent	Solvent	Temperature	Outcome
1 ^a	NaOH	H ₂ O/MeOH (2:1)	rt	No reaction
2 ^a	NaOH	H ₂ O/DMF (1:1)	60 °C	No reaction
3 ^a	NaOH	THF	reflux	No reaction
4	NaOAc	MeOH	reflux	No reaction
5	H ₂ O ₂ /NaOH	THF	rt	No reaction
6	PhSH/Et ₃ N	MeOH	rt	89%

a: Result obtained by M Anketell

*Table 10: Selected results for the attempted opening of epoxide **258***

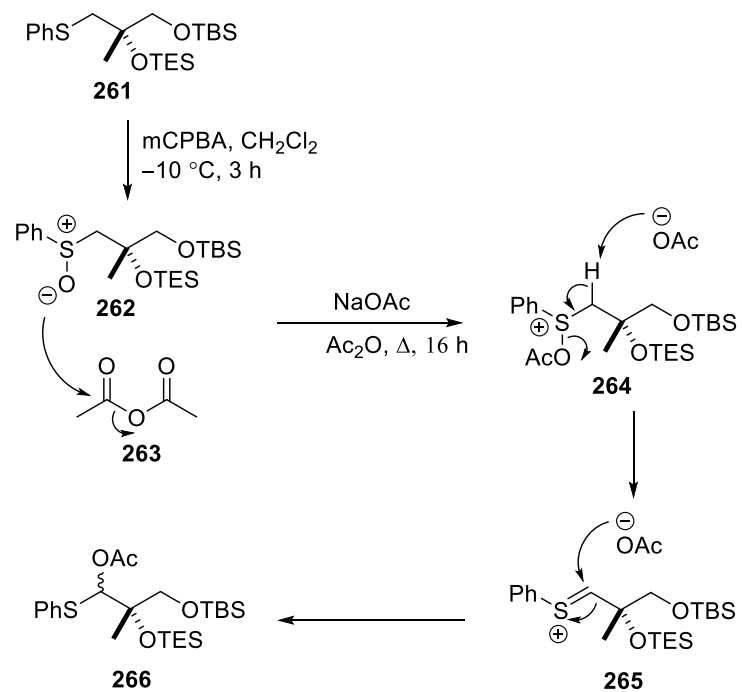
Both the crotylation and aldol strategies derive from the same key aldehyde intermediate **257**, so the synthesis of this fragment became the initial target. It was envisaged that the aldehyde could arise from the opening an epoxide, followed by protection and oxidation steps, with the key C₂₄ stereocentre being installed *via* the Sharpless asymmetric epoxidation of isobutenol.

4.2 Synthesis of the C₂₃-C₂₅ aldehyde

Work on the C₂₃-C₂₅ aldehyde was commenced in 2015 by Anketell¹²⁰ in close collaboration with the author. Drawing on the experience of our initial studies into the C₁-C₁₂ fragment, it was known that the synthesis of silyl-protected epoxy alcohol **258** was reliable and scalable, so this was deemed a suitable starting point.

With all eight stereoisomers of this fragment ultimately required, the choice of catalyst for the SAE⁷⁶ at this juncture was inconsequential. Sharpless epoxidation of isobutenol (using Ti(*i*-PrO)₄, (+)-DIPT and cumene hydroperoxide) with *in-situ* TBS protection proceeded smoothly to deliver the silyl-protected epoxy alcohol (**258**) in 70% yield (**Scheme 72**).

We postulated that under Lewis or Brønsted acidic conditions, it was likely that epoxide opening would occur at the C₂₄ position to give a tertiary carbocation. This would lead to a partial or complete loss of the enantiopurity developed in the first step. We therefore considered that this would necessitate the use of a basic nucleophile for the epoxide opening instead. Frustratingly, extensive attempts at opening the epoxide with a range of hydroxide and softer oxygen nucleophiles failed to afford any of the desired product. Treatment of the epoxide with sodium hydroxide (**Table 10, entries 1-3**) in a range of solvents and temperatures led only to the recovery of starting material. With the soft nature of the epoxide electrophile taken into account, some softer oxygen nucleophiles were trialled (**entries 4 and 5**), but similarly neither sodium acetate or sodium peroxide yielded any product. With sulfur based nucleophiles known to react well with epoxides, thiophenol in the presence of triethylamine was tried and gratifyingly provided the requisite thiohydrin. We envisaged that a Pummerer rearrangement could then be used to convert this sulphide into the desired aldehyde. Choice of solvent for the epoxide opening was found to be important. When the reaction was run in dichloromethane only a 50% yield of the product was obtained. However, a switch to a protic solvent (methanol chosen for ease of removal), enabled protonation of the ensuing tertiary alkoxide and gave the product in 89% yield.



Scheme 73: Mechanism of the Pummerer rearrangement

Protection of the tertiary alcohol, with TESOTf and 2,6-lutidine, proceeded smoothly generating the silyl ether in 97% yield. The Pummerer rearrangement^{121,122} can be used to convert sulfoxides into aldehydes. Oxidation of sulfide **261** into the prerequisite sulfoxide was somewhat hampered by overoxidation to the corresponding sulfone. Anketell obtained sulfoxide **262** in good yield (80%) through reaction with mCPBA at 0 °C, but with most of the remaining mass recovery being the sulfone. With overoxidation ostensibly rapid under these conditions, we surmised that lowering the temperature would diminish this. Gratifyingly, when the reaction was carried out at –10 °C, the desired sulfoxide was obtained in 88% yield, with only small amounts of the sulfone isolated (**Table 11, entry 2**).

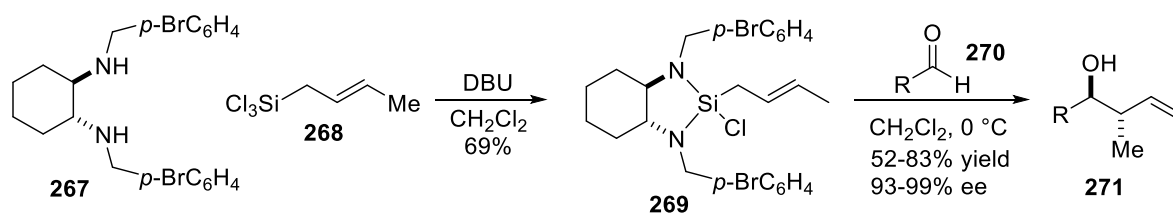
Sodium periodate has been shown to afford the oxidation of sulfides to sulfoxides selectively, without over-oxidation. Unfortunately, standard conditions in methanol and water (**entry 3**) led to no reaction; attributed to poor substrate solubility in the solvent mixture. Sodium periodate on silica gel in dichloromethane (**entry 4**) did show some conversion to product (and no over-oxidation), but the reaction proceeded very slowly and appeared to stall despite a large excess of reagent (20 equivalents). With neither of these alternative procedures providing an improvement on the optimised conditions with mCPBA, they were not pursued.

Entry	Reagent	Solvent	Temperature	Outcome
1 ^a	mCPBA	CH ₂ Cl ₂	0 °C	80%
2	mCPBA	CH ₂ Cl ₂	– 10 °C	88%
3	NaIO ₄	MeOH/H ₂ O	rt	No reaction
4	NaIO ₄ /SiO ₂	CH ₂ Cl ₂	rt	~30% conversion

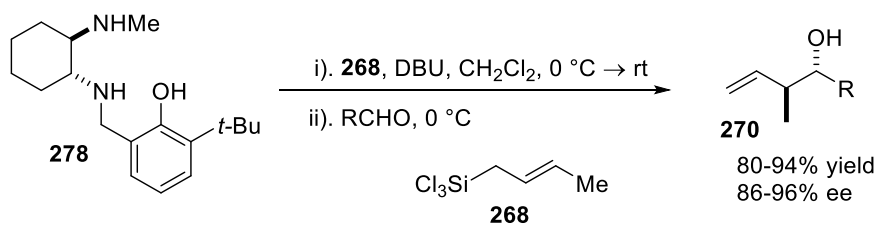
a: Result obtained by M Anketell

Table 11: Optimisation of selective sulfide oxidation

With sulfoxide **262** in hand, the Pummerer rearrangement proceeded under standard conditions of sodium acetate in refluxing acetic anhydride to give α -acetoxysulfide **266** as a mixture of diastereomers. The proposed mechanism proceeds as shown in **Scheme 73**.¹²³ The sulfoxide oxy-anion reacts with acetic anhydride to form S-acetate **264**. The α -proton can then be removed, with subsequent loss of the acetate, generating sulfonium species **265**. 1,2-attack of a second equivalent of acetate then produces the diastereomeric α -acetoxysulfides. The 1.2:1 ratio of epimers at this position is indicative of a small degree of stereoinduction from the OTES bearing α -stereocentre. This epimeric ratio is inconsequential however, with the stereocentre being eliminated in the following step. It does imply however, that any subsequent mismatched aldol or crotylation reactions employing reagent control, should overcome this inherent substrate control.

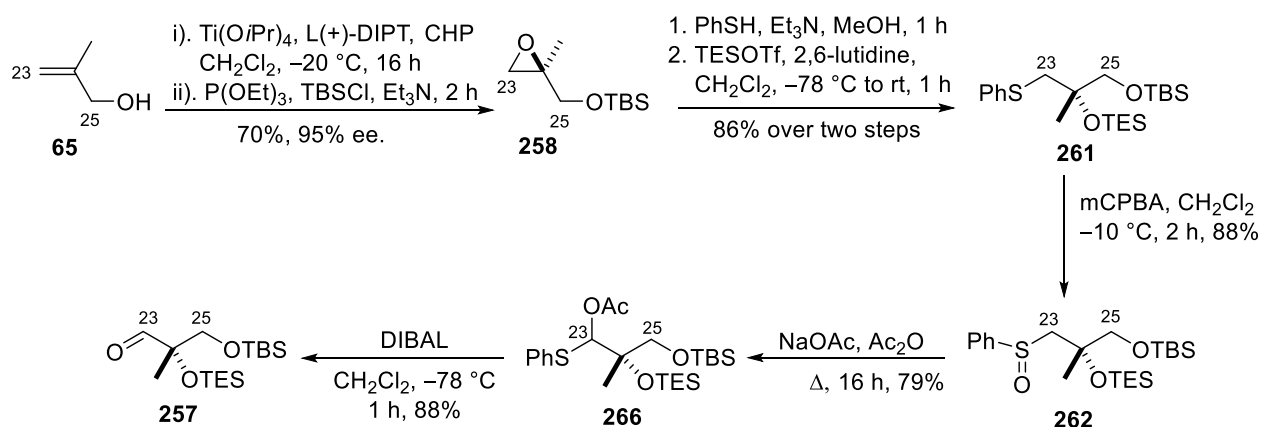


Scheme 78: Leighton's use of crotylsilanes for the highly enantio- and diastereo-selective crotylation of aldehydes



Scheme 79: Improved one-pot procedure developed by Leighton

Reduction of the acetate with DIBAL at $-78\text{ }^{\circ}\text{C}$, with subsequent collapse of the tetrahedral intermediate and loss of phenyl thiolate, revealed the desired aldehyde **257** in 88% yield. Maintaining a low reaction temperature was found to be crucial to avoid premature breakdown of the intermediate and subsequent over-reduction of the ensuing aldehyde (**Scheme 75**).



*Scheme 75: Final route to aldehyde **257** developed with Anketell*

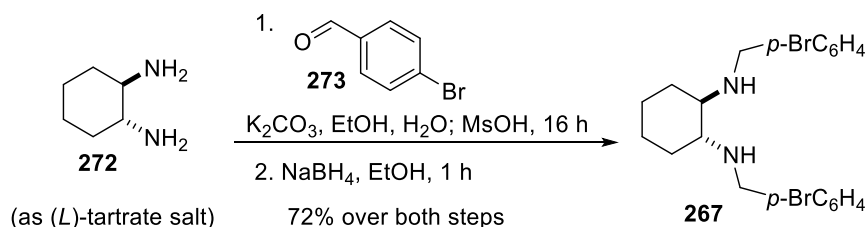
4.3 Initial Strategy *via* a Crotylation/Propargylation Route

4.3.1 Attempted Leighton Crotylation

With a route to aldehyde **257** established, attention turned to its conversion into the full fragment. Several crotylation procedures are detailed in the literature. Notably those by Brown^{124,125} and Roush,^{126,127} making use of chiral boranes and boronic esters respectively, are reported to proceed in good to excellent enantio- and diastereoselectivity. Unfortunately however, the lack of availability of the but-2-ene starting material renders these methods unviable. It has also been noted that the Brown methodology can suffer from an inability to fully overcome the inherent facial selectivity of chiral aldehydes.¹²⁸

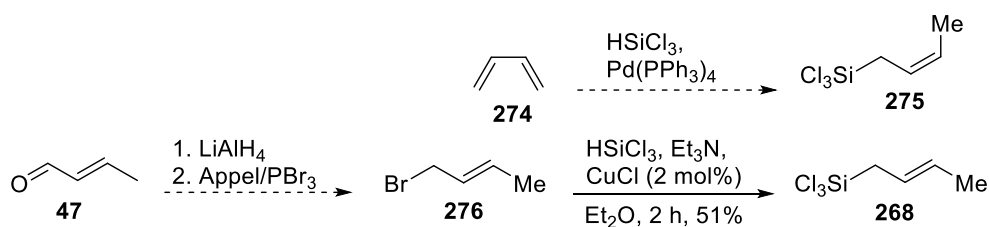
In 2004, Leighton published a highly enantio- and diastereoselective method for the crotylation of aldehydes employing a crotylsilane reagent based on a chiral diamine ligand.¹²⁹ *Bis*-amine **267** reacts with DBU and crotyl chlorosilane **268** to form the active catalyst **269**, which, whilst being relatively moisture sensitive, can be isolated. This then reacts with the aldehyde *via* an open transition state to give homoallylic alcohol **271** in modest to good yield and excellent enantioselectivity (**Scheme 74**). Diastereoselectivity is controlled by the *E/Z* ratio of the crotyl chlorosilane reagent. Moreover, control over this *E/Z* ratio and the diamine enantiomer used, allows all four possible product stereoisomers to be synthesised. Investigations into this route began with synthesis of *bis*-amine **267** and silane **26**.

The (*L*)-tartrate salt of (*R,R*)-1,2-diaminocyclohexane was treated with potassium carbonate in ethanol and water to produce the free amine *in situ* before the addition of *para*-bromobenzaldehyde and mesic acid. The resultant *bis*-imine was then reduced to the *bis*-amine to give **267** in 72% yield over both steps (Scheme 76).



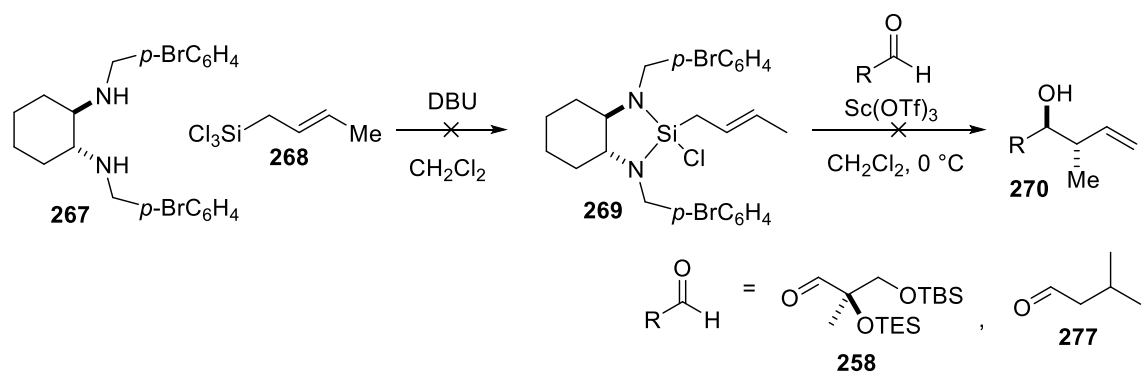
Scheme 76: Synthesis of *bis*-secondary amine **267**

Crotyl chlorosilane **268** was synthesised in a single step from crotyl bromide and trichlorosilane in the presence of triethylamine and catalytic copper (I) chloride. The *E/Z* ratio of the commercial crotyl bromide was a disappointing 3.7:1, but deemed acceptable for initial studies. Higher purity material could be made from the reduction and subsequent bromination of crotonaldehyde. The analogous (*Z*)-crotyl chlorosilane can be produced from butadiene with trichlorosilane and palladium (0) tetrakis(triphenylphosphine) (Scheme 77).



Scheme 77: Synthesis of crotylchlorosilane **268**

In 2011,¹²⁸ Leighton noted that the system previously reported in the literature, wherein the crotylation reagent and aldehyde are merely stirred together for 20 hours, is generally only successful in the cases where the aldehyde is aliphatic and sterically unhindered, giving no product at all in many other cases. A screen of Lewis acids was carried out, aimed at increasing the aldehyde reactivity whilst not degrading the enantioselectivity, with $\text{Sc}(\text{OTf})_3$ highlighted as the most amenable. Since aldehyde **257** has considerable steric bulk adjacent to the carbonyl, this appeared to be a critical development. Attempts by Leighton and co-workers to employ this as part of a one-pot procedure led to no catalysis, indicating an incompatibility between the DBU salts (more specifically the chloride ions) and the Lewis acid, deactivating the scandium (III) triflate.

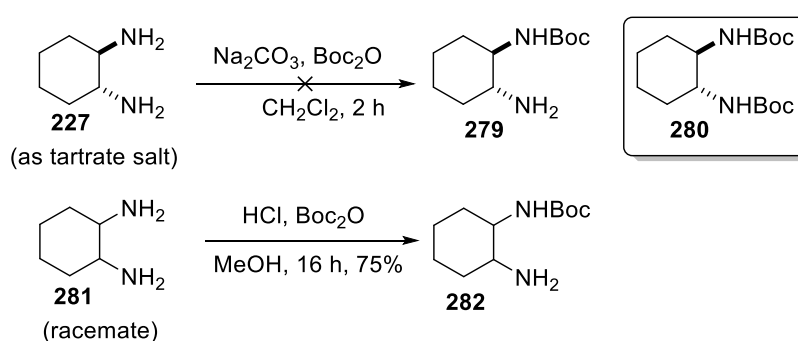


Scheme 74: Attempted crotylation of aldehydes **258** and **277** with crotyl silane **269** and Sc(OTf)_3

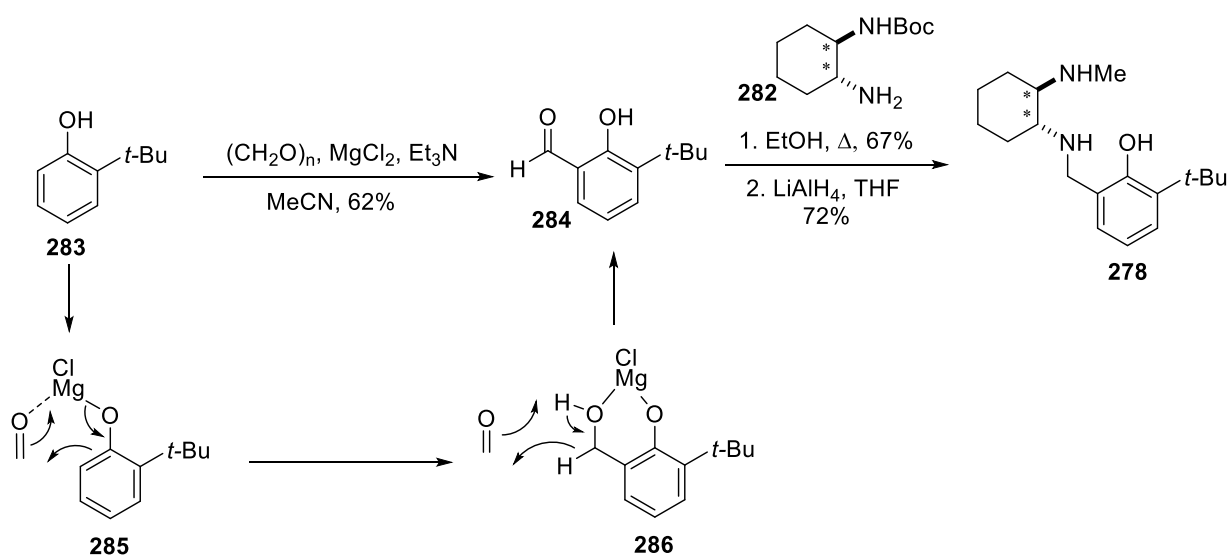
With amine **267** and silane **268** in hand, they were subjected to the reaction conditions with DBU in dichloromethane. The product was concentrated and redissolved in pentane to precipitate the DBU hydrochloride salts. This solution could then be submitted straight into the following reaction with the aldehyde and $\text{Sc}(\text{OTf})_3$. Both aldehyde **258** and the less sterically hindered valeraldehyde were tried, but without success (**Scheme 78**). Since the intermediate silyl chloride was not found to be amenable to purification, characterisation to determine its successful production is challenging. It was anticipated that dissolution in deuterated chloroform (even treated with molecular sieves) may be too wet to avoid degradation of the intermediate. Leighton notes that whilst the intermediate can be isolated and stored indefinitely, it is very moisture sensitive and should ideally be purified and stored in a glovebox. In our hands, without the appropriate apparatus, isolation was not deemed possible. After some perseverance and no positive results, this route was abandoned.

Leighton has also reported a more reactive catalyst system that doesn't require the use of a Lewis acid and can thus be employed in a one-pot procedure (**Scheme 79**).¹³⁰

The synthesis of the 2nd generation Leighton crotylation catalyst began, as previously, with (*R,R*)-diaminocyclohexane. Mono-protection of the diamine proved challenging. With the enantioenriched diamine **227** only available as the tartrate salt, standard conditions of HCl and di-*tert*-butyl decarbonate in methanol to afford mono-Boc protection proved ineffective. Treatment with sodium carbonate and di-*tert*-butyl dicarbonate led almost exclusively to the *bis*-Boc protected product **280** (alongside recovery of starting material). With the racemic diamine **281** available as the free amine, mono-protection proceeded smoothly, so this was carried forward as a means explore the later chemistry (**Scheme 80**).



*Scheme 80: Attempted mono-Boc protection of diaminocyclohexane **227***

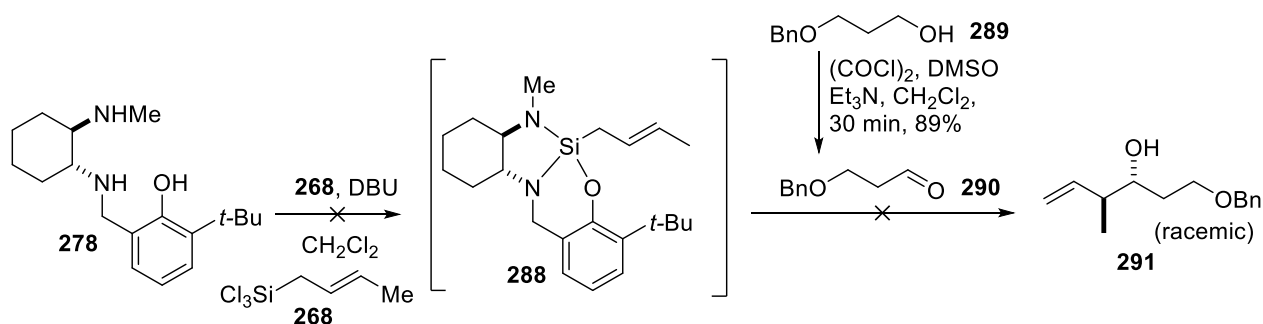


Scheme 81: Synthesis of 2nd generation Leighton reagent **278**

Treatment of 2-*tert*-butylphenol with paraformaldehyde, magnesium chloride and triethylamine gave aldehyde **284** in 62% yield. The reaction has been shown to effect selective *ortho*-formylation of phenols *via* the following mechanism.¹³¹ Deprotonation of the phenol, followed by trapping out with magnesium chloride gives oxy-magnesium species **285**, which can coordinate to formaldehyde, promoting addition at the *ortho* position. Following rearomatisation, the salicyl alcohol derivative can then undergo an Oppenauer oxidation to aldehyde **284** in a redox process using a second equivalent of formaldehyde (Scheme 81).

Condensation with racemic diamine **282** in refluxing ethanol, produced the corresponding imine, which was then reduced to the amine with concomitant reduction of the Boc protecting group to the N-methyl moiety, affording **278** in 48% over both steps.

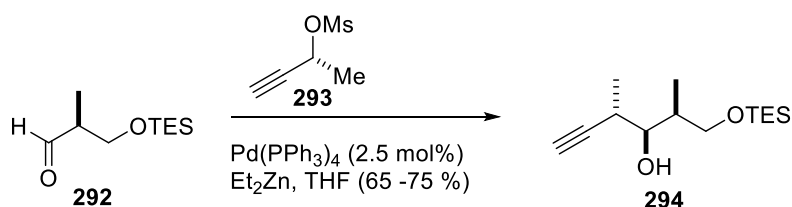
Alcohol **289** was oxidised under Swern conditions to afford aldehyde **290** in 89% yield for use as a model substrate. Disappointingly, despite several attempts at the crotylation reaction, no product was ever observed (Scheme 82). It was difficult to ascertain whether intermediate **288** ever formed, or if it wasn't reactive enough to afford the desired crotylation. Since this model aldehyde was significantly less sterically hindered than substrate **258**, it was deemed unlikely that this methodology would prove fruitful without a significant degree of optimisation.



Scheme 82: Attempted crotylation of aldehyde **290** with 2nd generation reagent

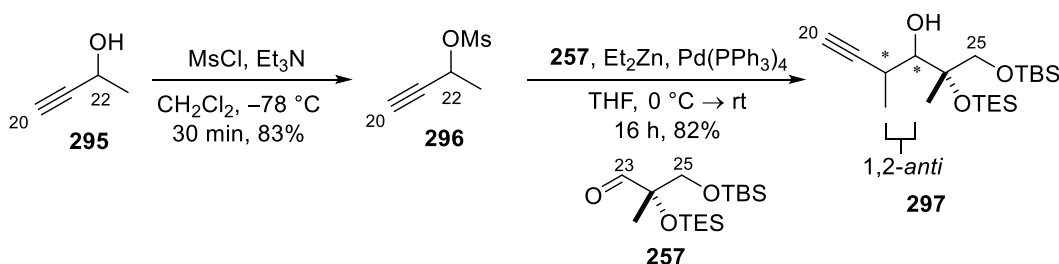
4.3.2 Marshall-Tamaru Propargylation Studies

With no positive results arising from the crotylation studies it became apparent that a different approach would be required. Once again inspired by Marshall's Discodermolide synthesis,¹³² an asymmetric propargylation was proposed. Marshall describes the treatment of Roche ester derived aldehyde **292** with asymmetric mesylate **293**, palladium (0) tetrakis(triphenylphosphine) and diethyl zinc to deliver homo propargyl alcohol **294** in good yield (**Scheme 83**).¹³² An attractive feature of the approach is the additional flexibility afforded with respect to the C₂₀-C₂₁ olefin functionality, and thus with C₁₉-C₂₀ fragment coupling. A Lindlar reduction^{133,134} of the alkyne should deliver the terminal olefin, amenable for a Heck coupling, whereas a hydrostannylation could alternatively provide the appropriate vinyl stannane for a Stille cross coupling.¹³⁵



*Scheme 83: Propargylation of aldehyde **292** in Marshall's synthesis of Discodermolide*

In order to test out the compatibility of the methodology with our substrate, the propargylation was initially attempted on racemic material. 3-butyn-2-ol was converted into mesylate **296** in 83% yield with mesyl chloride and triethylamine at -78°C . Exposure of the mesylate to diethyl zinc and palladium (0) tetrakis(triphenylphosphine), followed by the addition of aldehyde **258** afforded the homopropargylic alcohol in a pleasing 82% yield (**Scheme 84**). Due to the racemic nature of the mesylate used, the product was isolated as a 1:1.4 ratio of *anti*-diastereomers across the C₂₂-C₂₃ bond. This observed diastereoselectivity for the reaction can be attributed to the facial selectivity of the aldehyde, with the result comparable to that observed during the Pummerer rearrangement described in **section 4.2**. This inherent substrate selectivity was deemed small enough to be overcome by reagent control.



*Scheme 84: Racemic mesylate formation and propargylation with aldehyde **258***

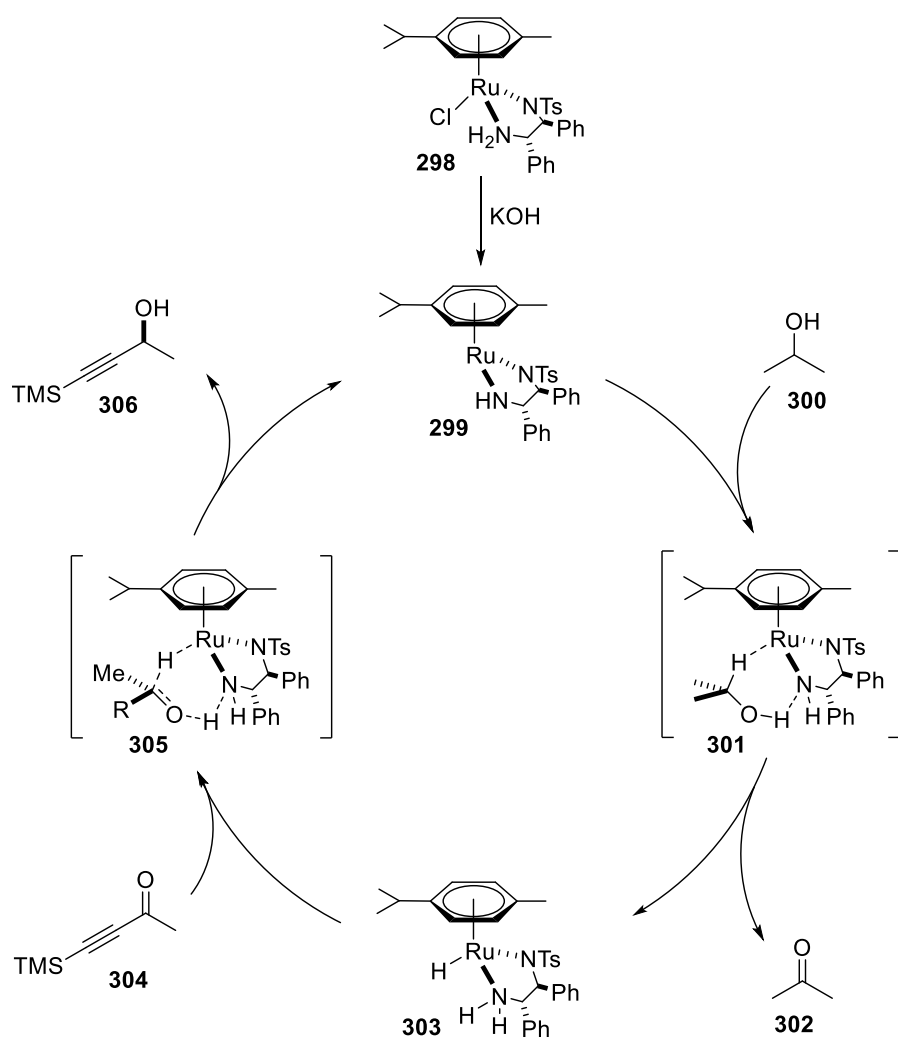
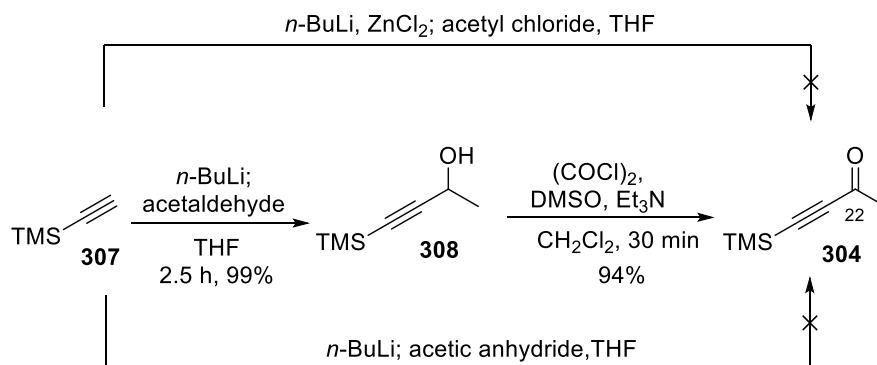


Figure 28: Proposed catalytic cycle for Noyori transfer hydrogenation

With this promising result, attention turned to the synthesis of the appropriate enantioenriched mesylate. A survey of the literature highlighted a Noyori reduction of the corresponding ketone as the most common route to these chiral mesylates. In 1997, Noyori reported the asymmetric reduction of acetylenic ketones *via* transfer hydrogenation utilising a ruthenium catalyst with a chiral diamine ligand and *i*-PrOH as a hydrogen source.¹³⁶ Prior to this, no chemo- and regioselective asymmetric hydrogenation had been published. He noted however, that whilst this reduction was not amenable to terminal alkynes, silyl protected alkyne **304** could be reduced in 99% yield and 98 %ee. 2-propanol is reported to be the best hydrogen donor for these acetylenic ketones. Whilst a 1:1 mixture of formic acid/triethylamine is known to afford numerous other transfer hydrogenation products, on these systems it delivered the products in only ~55% yield.

The proposed mechanism proceeds as shown in **Figure 28**. Ruthenium complex **299** can either be isolated and stored prior to use, or generated *in situ* from the treatment of the corresponding ruthenium chloride (**298**) species with potassium hydroxide. Initial coordination of 2-propanol to complex **299** followed by concerted hydrogen transfer and formation of dihydride species **303**, generates acetone as the by-product. Coordination of the ketone starting material then produces intermediate **305** delivering dihydrogen across the carbonyl to afford the enantioenriched secondary alcohol **306**. The enantioselectivity is derived from the chirality of the diamine ligand. Favourable CH- π interaction between the polyalkylated arene and, in this case, the π -bonds of the substrate alkyne, enhance the steric interactions with the chiral ligand.¹³⁷ Notably, neither the ketone or the alcohol are proposed to coordinate to the metal directly.

Several routes to propargylic ketone **304** were considered. Brandsma and coworkers describe the acetylation of terminal alkynes using *n*-BuLi, zinc (II) chloride and acetyl chloride.¹³⁸ Unfortunately, in our hands this protocol failed to give any product, possibly attributable to acetic acid being present in the acetyl chloride, quenching out the anion intermediate (**Scheme 85**).



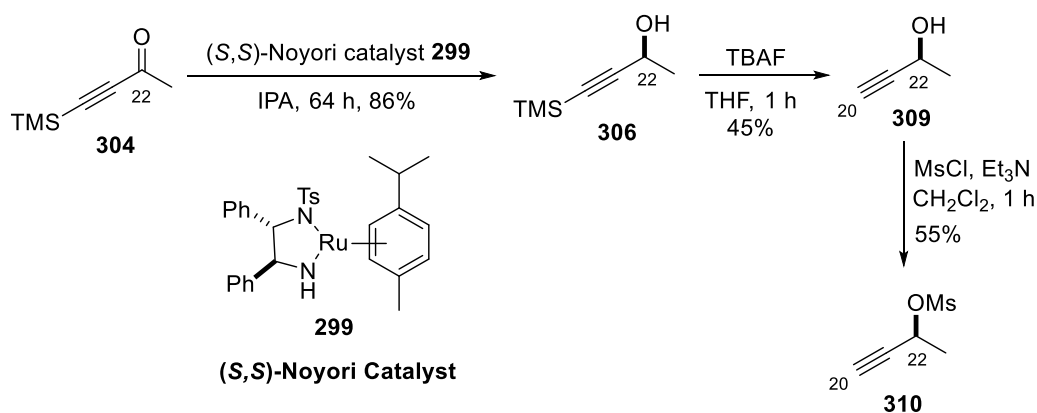
Scheme 85: Synthesis of acetylenic ketone **304**

Furthermore, reaction of the pre-formed anion with acetic anhydride failed to give any product. At this point, a two-step procedure was considered, wherein the anion would be trapped out with acetaldehyde, giving propargylic alcohol **308**, and was subsequently subjected to Swern oxidation conditions, to afford the desired ketone. Pleasingly, this delivered **304** in 93% yield over both steps. Propargylic alcohol **308** was also synthesised in 85% yield from but-3-yn-1-ol, *via* a double deprotonation, silyl protection and silyl ether deprotection procedure, as preceded on propargyl alcohol in **section 3.3.2**.

With ketone **304** in hand, attention turned to an asymmetric reduction to install the C₂₂ stereocentre (**Scheme 86**). Ruthenium complex **299** was kindly donated by Adam Yip. On small (25 mg) scale, the reaction proceeded smoothly, providing the enantioenriched alcohol in 86% yield. ¹⁹F NMR analysis carried out on the Mosher esters of the corresponding TIPS alkyne determined an excellent 97% e.e, in line with literature values.¹³⁶

In our hands however, the reaction had disappointing scalability. The reaction repeatedly stalled, although even with the re-isolated ketone, mass recovery was poor. Attempts made to alleviate this by portionwise addition of the catalyst, were only modestly successful.

Hampered by the volatility of alcohol **309**, the silyl deprotection proved challenging. Due to the scale issues with the previous step, the product was never obtained in significant enough quantities to facilitate distillation. Deprotection under standard conditions with TBAF in THF gave the product in 45% yield. Unfortunately, switching to the more volatile Et₂O failed to give any product and potassium carbonate in methanol also only delivered the terminal alkyne in 52% yield (albeit on small scale). Mesylation of the resultant alcohol proceeded smoothly, providing mesylate **310** in 55% yield.



Scheme 86: Noyori reduction of ketone **304** and subsequent elaboration into non-racemic mesylate **310**

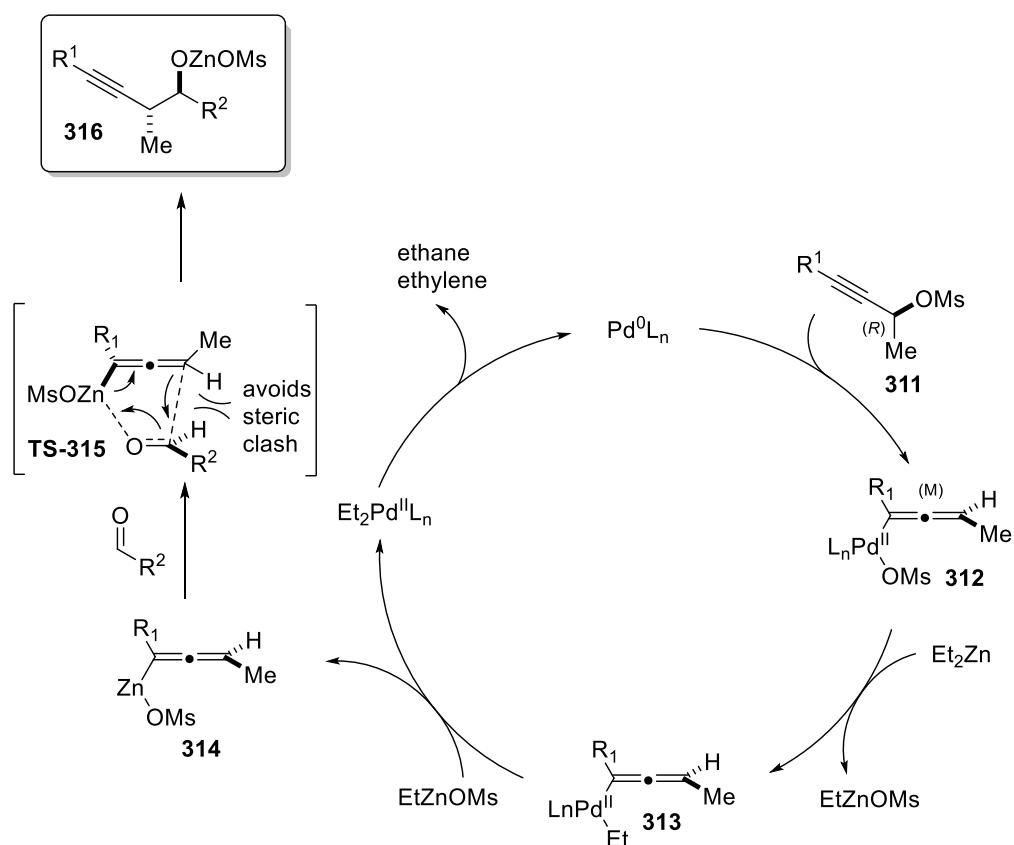
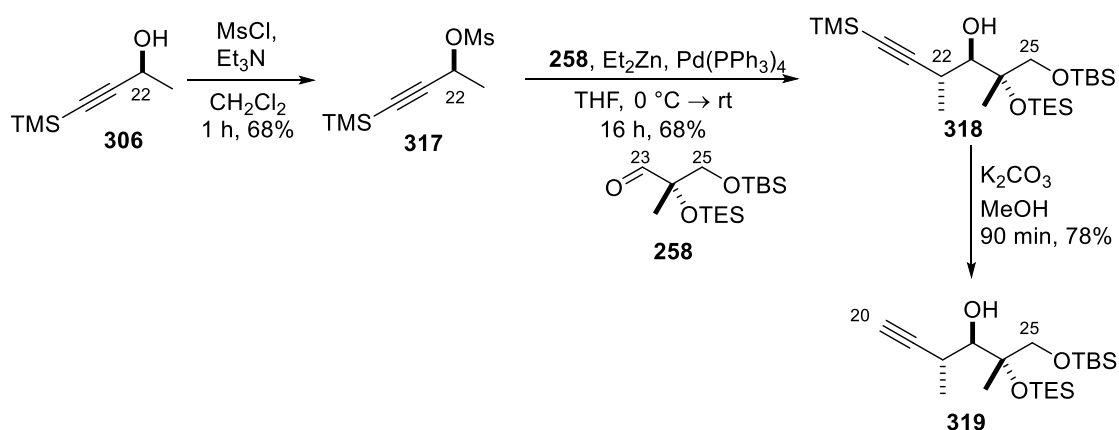


Figure 29: Proposed reaction mechanism for the propargylation of aldehydes

Due to the low yield for the deprotection step, an alternative strategy was considered, wherein the silyl removal could take place post Marshall propargylation. Alcohol **306** was treated with mesyl chloride and triethylamine delivering mesylate **317** in 68% yield. Subjection of this to diethyl zinc and aldehyde **258** in the presence of palladium (0) tetrakis(triphenylphosphine) gratifyingly gave homopropargylic alcohol **318** in 68% yield as a single product by NMR. The alkynyl silane could then be removed by treatment with potassium carbonate in methanol in 78% yield (**Scheme 87**). Although the overall yield for this sequence remained lower than for the racemic version, it represented a sufficient improvement on the previous route *via* mesylate **310**, due to its better scalability.

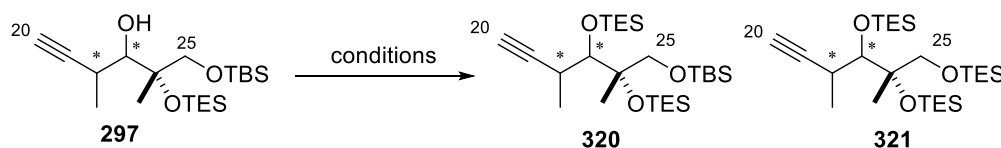


Scheme 87: Modified propargylation with delayed silyl deprotection

The propargylation is proposed to proceed *via* the following mechanism (shown in **Figure 29**). Oxidative insertion of the palladium into the alkyne, with displacement of the mesylate gives allenyl intermediate **312**. Diethylzinc then carries out a ligand exchange on palladium to provide species **313**, which can then undergo transmetalation forming diethyl palladium (II) and allenyl zinc species **314**. The aldehyde then coordinates to this allenyl zinc species, promoting nucleophilic attack, affording the *anti*-propargylation product **316**. The aldehyde reacts selectively from the lower face of the chiral allenyl species, to avoid β -hydride elimination and ligand dissociation of the diethyl palladium releases ethane and ethylene providing palladium (0) to re-enter the catalytic cycle.

With propargylation product **319** in hand, it was envisaged that the desired fragment could be obtained *via* a straightforward silyl protection of the newly formed alcohol, followed by a Lindlar reduction of the terminal alkyne. Initial investigations were carried out on the diastereomeric mixture of homopropargylic alcohols **297**. Disappointingly, the requisite silyl protection proved more challenging than expected. Treatment of the secondary alcohol with TESOTf and 2,6-lutidine led to significant levels

of deprotection of the primary TBS (**Scheme 88**). We attributed this to the putative presence of triflic acid, produced by small levels of aqueous quenching of the TESOTf. With this process seemingly occurring at a similar rate to the secondary alcohol protection, the resulting free primary alcohol could undergo TES protection, producing a product mixture of differentially protected primary alcohols.



Scheme 88: Attempted protection of diastereomeric alcohol 297

Numerous attempts were made to alleviate this issue. Addition of a large excess of 2,6-lutidine failed to prohibit the deprotection (**Table 12, entry 2**), indicating that the Lewis acidity of the TESOTf may be the contributing factor instead. Attempted protection with TESCl, imidazole and catalytic DMAP (**entry 3**) proved unreactive and failed to provide any product. Disappointingly, the same conditions with triethylamine and stoichiometric DMAP failed to provide any improvement. A fresh bottle of TESOTf (**entry 5**), provided a significant improvement in the product ratio, but with sufficient deprotection still observed, this was not deemed a reasonable solution. At this junction, the protecting group strategy was reconsidered and, since the C₂₃ alcohol would need to be deprotected prior to the C₂₄ or C₂₅ alcohols, a TMS at this position should both survive the intermediate reaction conditions and be easier to selectively deprotect. With the TMSCl significantly less Lewis acidic than TESOTf, but sufficiently more reactive than TESCl, the protection proceeded smoothly, giving TMS silyl ether **322** in 80% yield.³

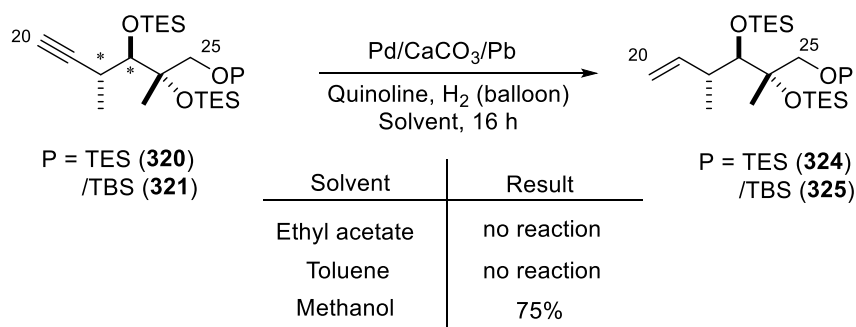
Entry	Silylating agent	Equiv. silylating agent/base	Temperature	Product ratio 320:321	Yield
1	TESOTf, 2,6-lut.	1.2 / 1.5	–78 °C	0.7:1	72%
2	TESOTf, 2,6-lut.	1.1 / 1.8	–78 °C	0.6:1	58% (88 brsm)
3	TESCl, imid., DMAP	1.2 / 1.5 / 0.05	rt	N.a.	No reaction
4	TESCl, Et ₃ N, DMAP	1.5 / 2.0 / 2.0	rt	N.a.	No reaction
5	TESOTf, 2,6-lut. ^a	1.5 / 2.0	–78 °C	1.9:1	86%
6	TMSCl, imidazole	1.5 / 2.5	rt	100% 322	80%

a: New bottle of TESOTf used

Table 12: Selected conditions attempted for the protection of alcohol 297

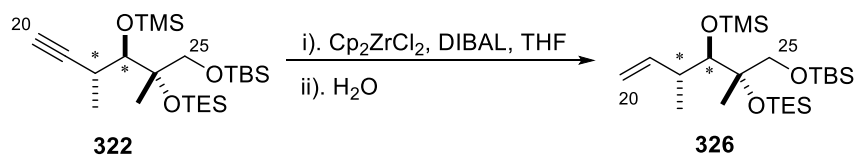
³ These conditions were later carried out on the single diastereomer **319**, giving TMS ether **323** in 82% yield.

Using diastereomeric alkynes **320** and **321** (With P= 1.9:1 TES/TBS), a solvent screen was carried out to determine the optimum conditions for the Lindlar reduction (**Scheme 89**). Whilst ethyl acetate and toluene failed to give any product, methanol delivered the product alkenes (**324** and **325**) in good yield (75%). Frustratingly though, the reaction proved to be capricious, frequently stalling. Resubmission to the reaction conditions required purification of the crude material to be effective, but despite this, pushing the reaction to 100% completion was challenging.



*Scheme 89: Solvent screen for the Lindlar reduction of alkynes **320** and **321***

An alternative reduction procedure was explored, following a hydrozirconation protocol. Generation of the reactive zirconium hydride species (Schwarz reagent) *in situ* can be achieved by the pre-mixing of zirconocene dichloride and DIBAL. Although in this case the regiochemistry of the hydrozirconation product obtained is inconsequential, the major product predicted would be the terminal vinyl zirconium moiety. This species can be trapped out with a variety of nucleophiles, but quenching with water should afford the terminal unfunctionalized alkene. Although this reaction was only attempted on small scale, a similar result to the Lindlar reduction was obtained, with a 65% conversion observed (**Scheme 91**).



*Scheme 90: Attempted reduction of alkyne **322** via a hydrozirconation*

With the difficulties encountered with the scalability of the Noyori reduction and the conversion rates of the alkyne reduction, a new strategy to construct the C₂₂-C₂₃ bond was sought.

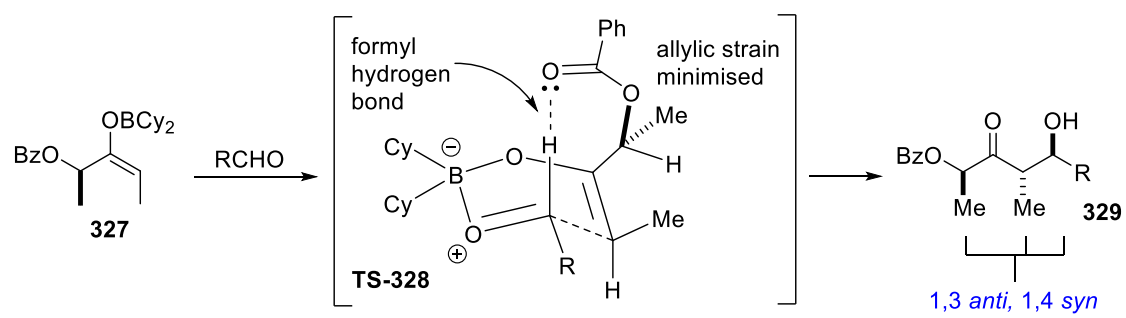


Figure 30: Preferred transition states for benzoyl protected enolates

4.4 Revised Approach to C₂₀-C₂₅ Fragment *via* an Aldol Coupling Strategy

4.4.1 Titanium Aldol Approach to Aldol Adduct 254

With both the crotylation and propargylation routes failing to provide the final fragment in good yield, the alternative strategy detailed in **section 4.1** was pursued, based on an aldol approach. It was envisaged that access to each of the eight different stereoisomers of the fragment could be made *via* either an Evans *syn* aldol or *anti* aldol using a lactate derived ketone.

With lactate derived ketones, the enol borinate geometry is determined by the availability of the α' -oxygen centre. In the benzoyl case, the α' -oxygen lone pair is delocalised as part of the ester, so is not available to coordinate to boron. A similar transition state to that described for the Roche ester derived ketones is observed. A favourable hydrogen bonding interaction between the α -proton on the ethyl group and the chloride, ensures that the boron preferentially lies on the side of the ethyl group. This interaction also increases the acidity of the other α -proton, leading to (*E*)-enolate formation (**Figure 31**).

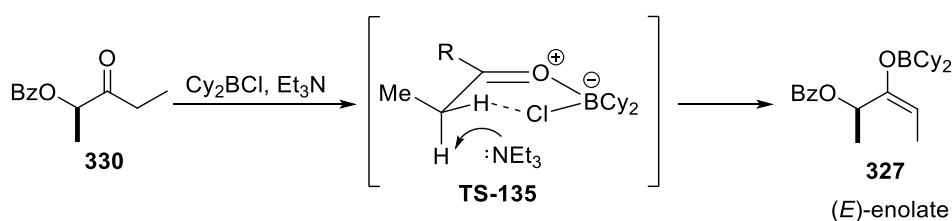


Figure 31: Selective lactate-derived (*E*)-enolate geometry using a benzoyl protecting group

It is proposed that the transition state for the aldol reaction adopts a boat conformation (**Figure 30, TS-328**).⁹² The π -facial selectivity of the enolate is dictated by the minimisation of allylic strain, placing the α -proton eclipsing the enolate olefin. The excellent diastereoselectivity typically observed in these reactions can be attributed to the carbonyl of the benzoyl group having sufficient reach to chelate internally, forming a favourable formyl hydrogen bond to the aldehydic proton. This leads to the 1,3-*anti*, 1,4-*syn* diastereomer as the major product.

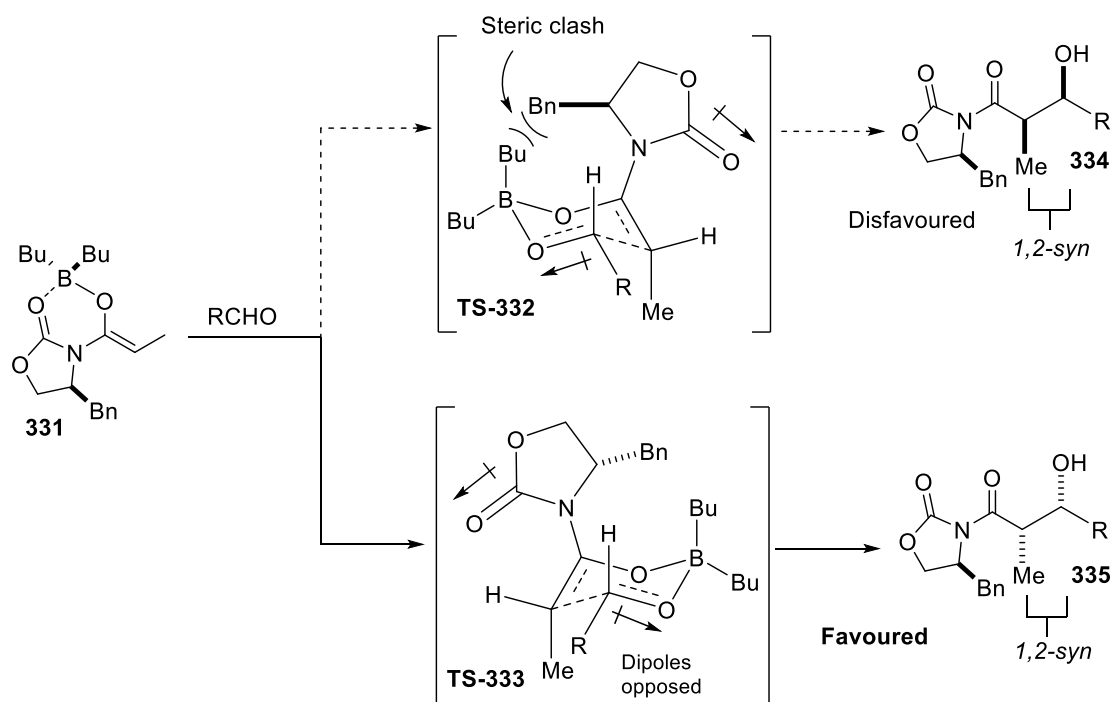


Figure 32: Transition state for the Evans syn aldol

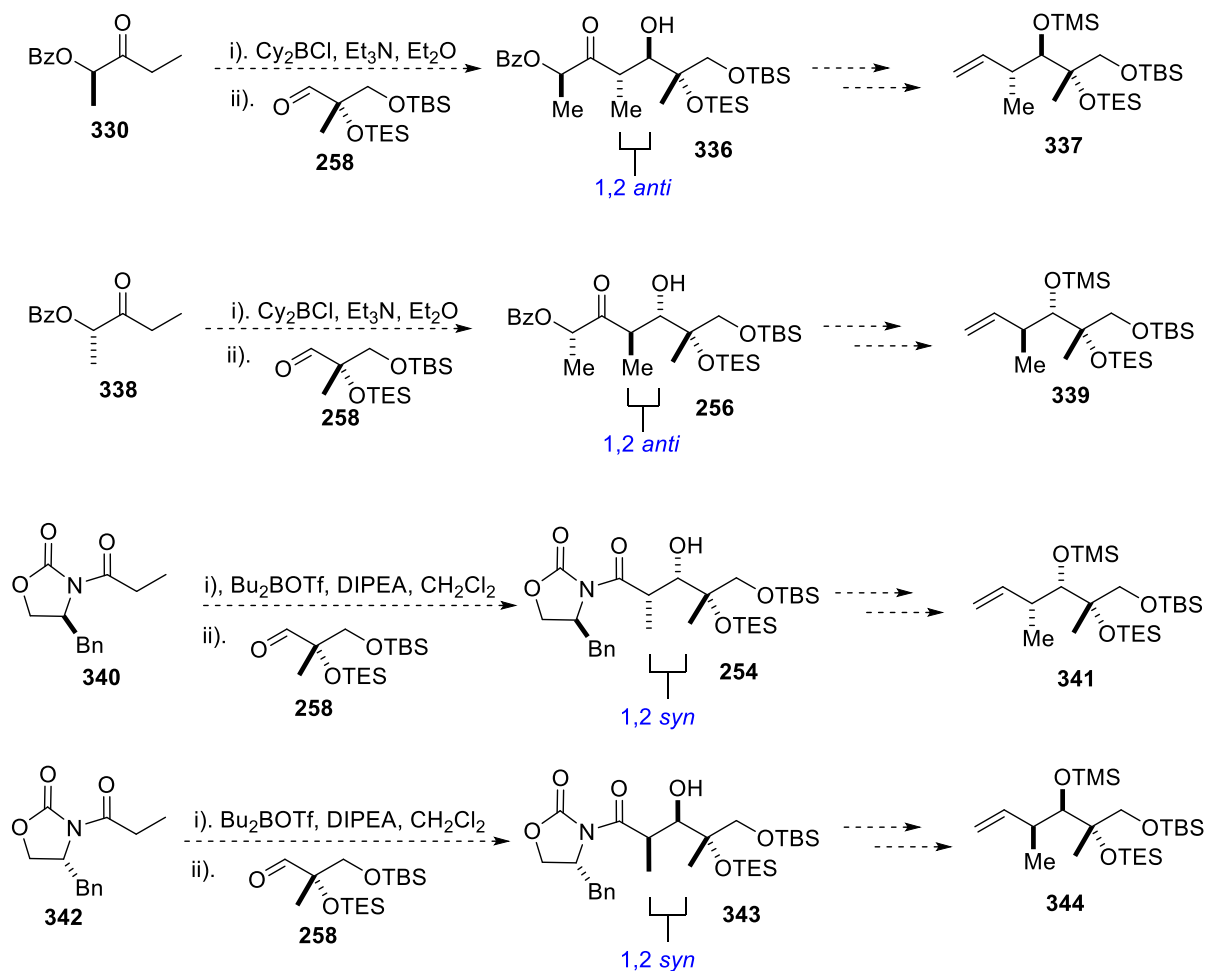


Figure 33: Proposed access to all four possible C_{21} - C_{22} diastereomers

The Evans auxiliary can be derived from phenylalanine (or valine for the isopropyl variant) in 3 steps. Since all eight stereoisomers will ultimately need synthesising, both enantiomers of the auxiliary are required. For initial studies to explore the route though, use of the natural enantiomer (*L*)-phenylalanine was chosen. For these studies, the auxiliary was kindly donated by Matthew Anketell.

As discussed in **section 2.3.1**, the selective enolisation of carbonyl species has been well documented. The small ligands and good leaving group of dibutylboron triflate lead to the formation of the (*Z*)-enol borinate, as shown in **Figure 34**. Preliminary chelation of the Lewis acid between the two carbonyls affords intermediate **345**. Deprotonation occurs from above to avoid steric clashing of the bulky base with the benzyl group, with the proton being removed, orientated perpendicular to the carbonyl to maximise overlap between the C-H σ and C=O π^* orbitals. In one conformation, there is a destabilising interaction between the oxazolidinone ring and the methyl group, which is not present in the other, lower energy, conformer.

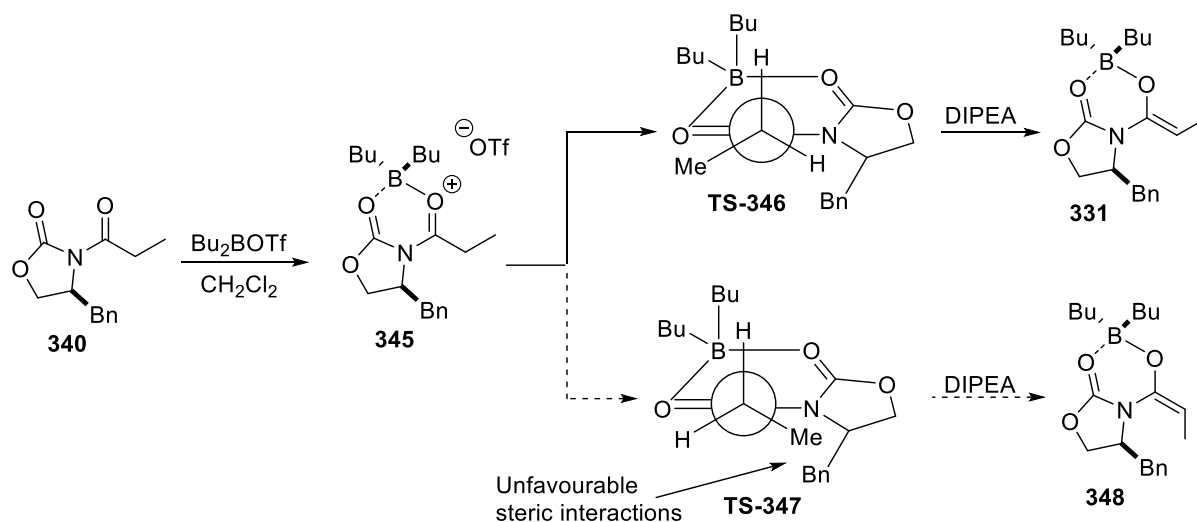


Figure 34: Rationale for selective Evans auxiliary enolate formation

The aldol reaction is known to take place *via* a Zimmerman-Traxler type transition state. The (*Z*)-enol borinate therefore leads to the two possible products being the respective 1,2-*syn* aldol adducts. The enantioselectivity is derived from the chiral auxiliary. With dipoles opposed, the lower energy transition state (**Figure 32, TS-333**) places the bulky benzyl group facing outwards, selectively delivering the *syn* product in which the alcohol and methyl group lie on the opposite face to the benzyl.

Between the 'lactate' and Evans' aldols shown and those for the epimeric lactate starting materials, all four product stereoisomers are obtainable (**Figure 33**). Both lactate and Evans 'auxillaries' can be readily converted to useful functional groups through a series of simple transformations. In the lactate case,

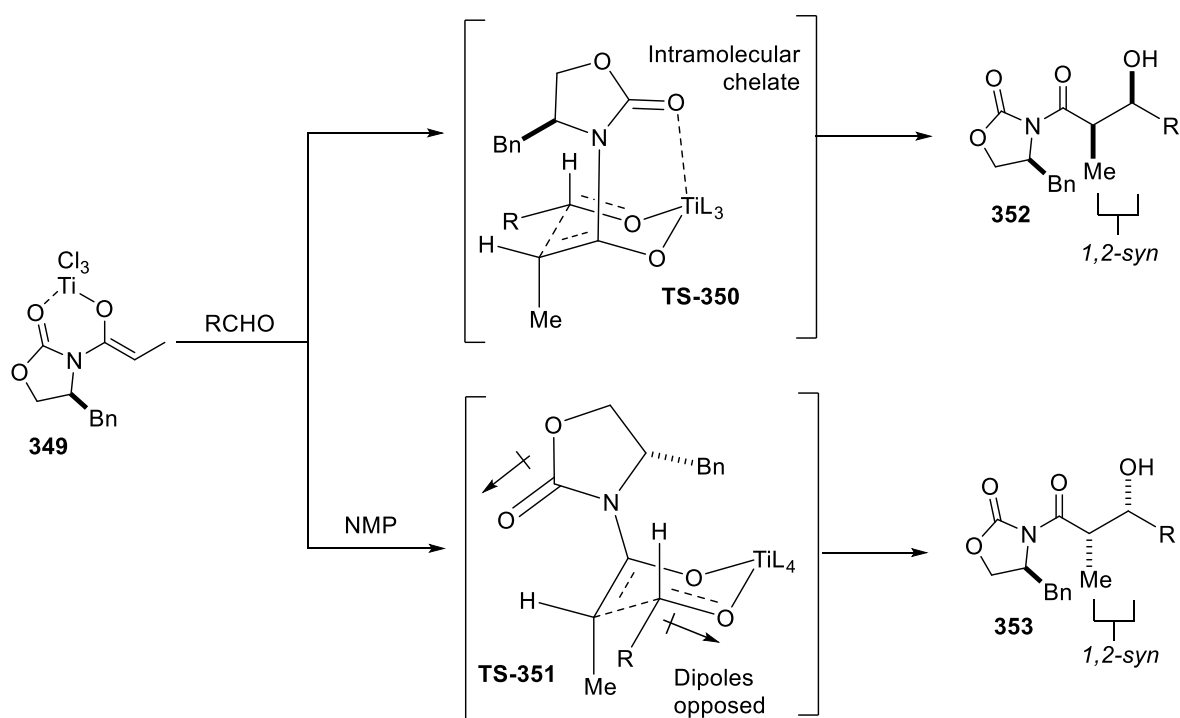
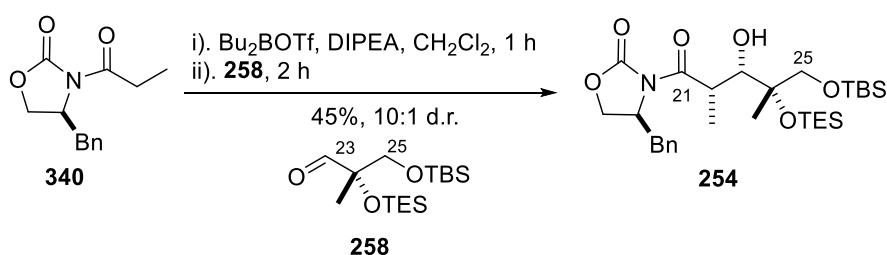


Figure 35: Transition state for the Crimmins syn aldol

concomitant reduction of the benzoate ester and ketone, followed by a periodate cleavage should afford aldehyde precursors from which terminal alkenes **337** and **339** can be accessed. In the Evans auxiliary case, the oxazolidone derivative can be cleaved by reaction with lithium hydroxide, sodium methoxide or lithium borohydride, revealing the corresponding carboxylic acid, ester or alcohol respectively, from which the appropriate oxidation or reduction and Wittig olefination reactions, should provide alkene **341** or **344**.

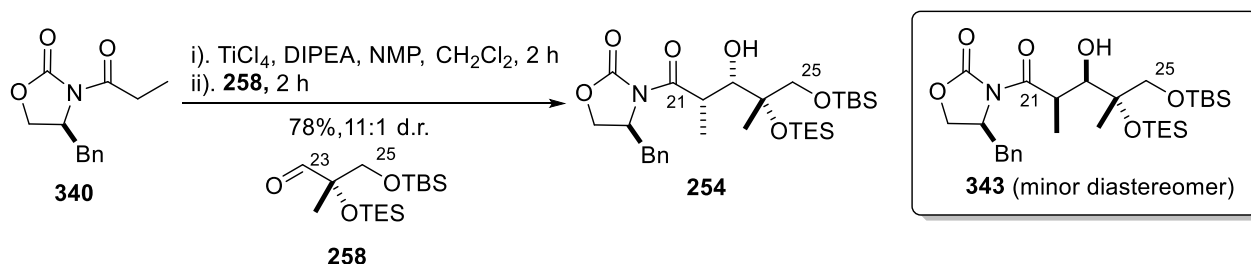
Unfortunately, standard Evans aldol conditions of dibutylboron triflate and DIPEA furnished aldol adduct **254** in only 45% yield (**Scheme 91**). This was attributed to poor reagent quality of the dibutylboron triflate, despite it being freshly distilled. The diastereoselectivity was an acceptable 10:1 d.r.



*Scheme 91: Dibutylboron triflate-mediated aldol with Evans auxilliary **340***

A search through the literature identified a paper,¹³⁹ in which Crimmins describes an alternative procedure for the asymmetric addition of oxazolidinone propionates to aldehydes, mediated by titanium tetrachloride. Previous protocols had suffered from poorer diastereoselectivities with respect to the dibutyl enol borinates and required a significant excess (2-5 equiv.) of the aldehyde for the reaction to reach completion. In 1998,¹⁴⁰ Crimmins reported an improved method using 1.0 equiv. of titanium tetrachloride and 2.2 equiv. of (–)-sparteine to afford the titanium enolates. It was proposed that the second equivalent of sparteine was required as an additional ligand for titanium, ensuring that there were no free sites on the titanium for chelation of the auxiliary. The supply issues with sparteine however, necessitated the development of a second-generation protocol. In 2004,¹³⁹ Crimmins described the use of 1.05 equiv. of titanium tetrachloride, 1.1 equiv. of DIPEA and 1.0 equiv. of NMP to form the requisite titanium enolate, reporting a 99% yield and 97:3 d.r. in the reaction between oxazolidinone **340** and isobutyraldehyde (**Figure 35**).

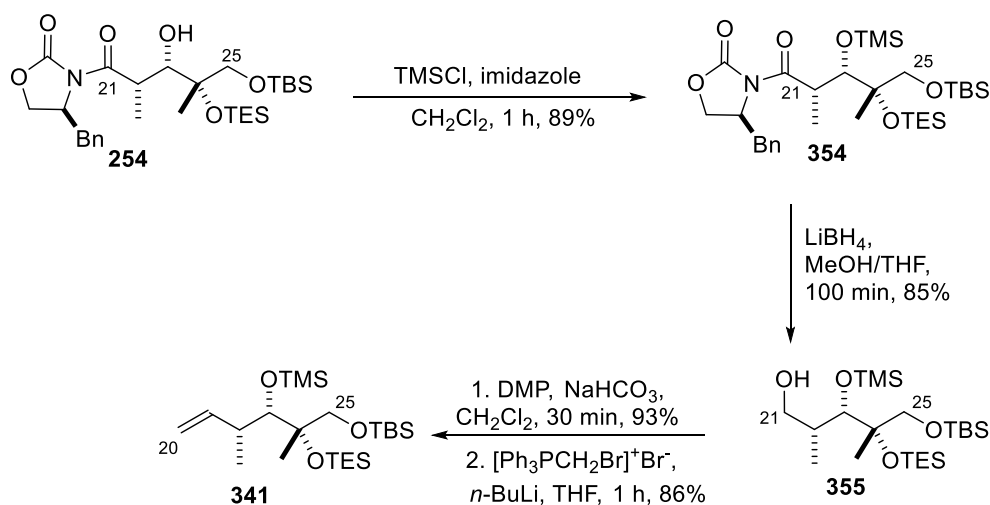
Pleasingly, this protocol afforded aldol adduct **254** in 78% yield and 11:1 d.r. (**Scheme 92**). A diastereoselectivity similar to the equivalent dibutylboron enolate was obtained, with a significant improvement in yield and reliability of the reaction.



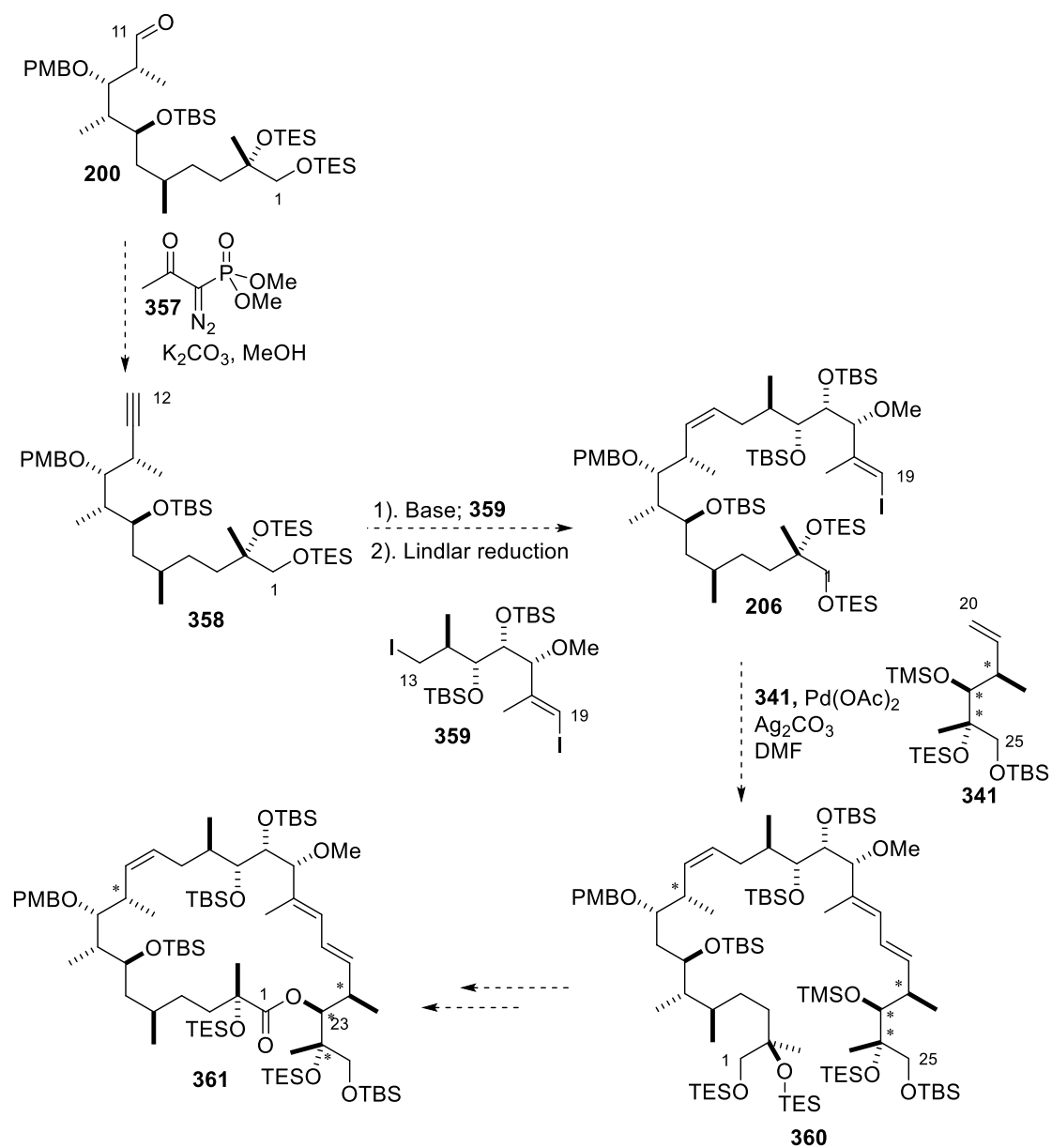
*Scheme 92: Titanium-mediated aldol with Evans auxilliary **340***

4.4.2 Auxiliary Cleavage and Elaboration of C₂₀ Terminus

As with the propargylation product, aldol adduct **254** was protected as the C₂₃ TMS ether with TMSCl and imidazole, affording the product in good yield (89%, **Scheme 93**). Auxiliary cleavage with sodium *bis*-(methoxyethoxy)aluminium hydride to give the corresponding aldehyde in a single step, as preceded by Shin and coworkers in their synthesis of Dictyostatin¹⁴¹ was attempted, but without success. Reaction with sodium methoxide to give the corresponding methyl ester was also tried, but despite the addition of a large excess of reagent, the reaction proceeded very slowly. Fortunately, a reductive cleavage with lithium borohydride in the presence of methanol delivered alcohol **355** smoothly in 85% yield. Oxidation with Dess-Martin periodinane furnished the aldehyde (**356**) in 93% yield, which was then submitted to a Wittig olefination protocol, affording terminal alkene **341** in 86% yield.



*Scheme 93: Elaboration of aldol adduct **254** into completed C₁₃-C₁₉ fragment **341** (the Heck substrate)*



*Scheme 94: Initial proposed fragment union strategy to form macrocycle **361***

Chapter 5: Results and Discussion – Part IV

Macrocycle endgame

5.1 Formation of the C₁₂–C₁₃ Bond

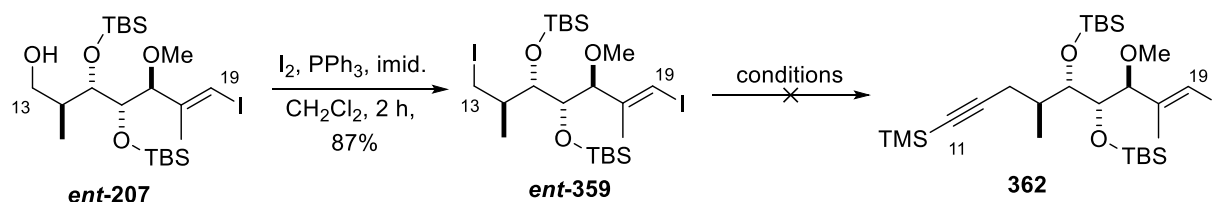
5.1.1 Initial Strategy *via* an Acetylide Addition Approach

With three of the unknown stereocentres lying in the C₂₀–C₂₅ fragment, it was envisaged that the most concise route to the eight completed macrocycles would involve the formation of a C₁–C₁₉ fragment (**206**), which could be reacted in turn with the eight different C₂₀–C₂₅ fragment stereoisomers (e.g. **341**). The diastereomeric C₁–C₂₅ linear fragments generated, could then be converted into the desired macrocycles in five steps (**Scheme 94**).

To this end, a strategy was required in which the C₁₂–C₁₃ bond could be formed before the C₁₉–C₂₀ bond. After attempts to mask the C₁₉ vinyl iodide as a vinyl silane had proved fruitless, an alternative strategy was devised. Of particular importance, any C₁₂–C₁₃ bond forming reaction would need to be compatible with the vinyl iodide, obviating the use of any palladium-catalysed methods.

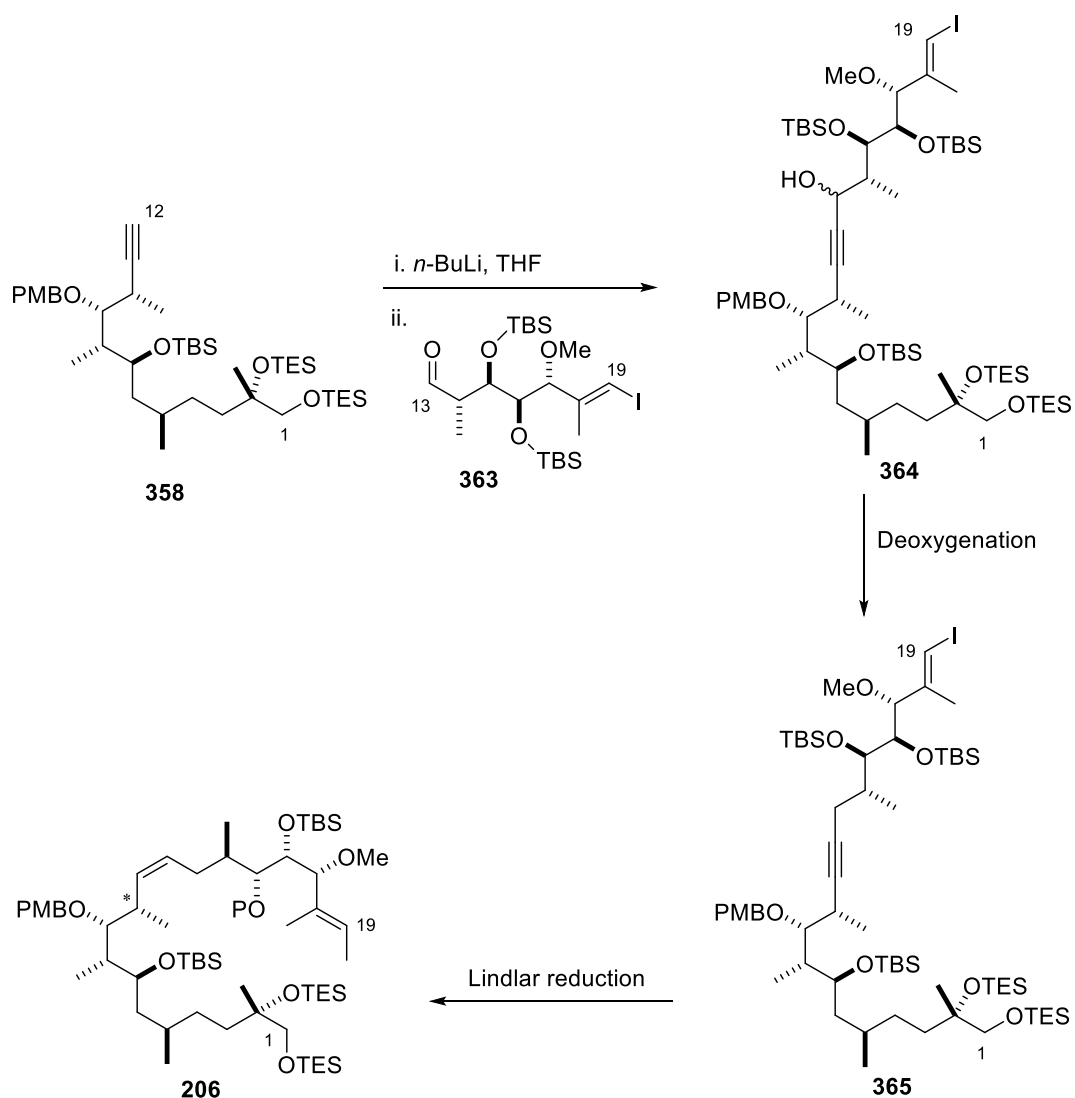
With this in mind, it was proposed that aldehyde **200** could be converted into terminal alkyne **358** *via* a Seyferth-Gilbert homologation,^{61,62} using the Ohira-Bestmann modification⁶³ (or alternatively *via* a Corey-Fuchs olefination reaction).⁶⁵ Deprotonation at the terminal position could form a nucleophile which could participate in an S_N2 displacement of iodide **359** (in turn formed from alcohol **207**). Lindlar reduction of the resultant alkyne, would give (Z)- alkene **206**.

To investigate this proposed strategy, a model system was synthesised (**Scheme 95**). The enantiomeric C₁₃–C₁₉ fragment **ent-207** was converted into iodide **ent-359** under Appel conditions¹⁴² (I₂, PPh₃ and imidazole) in good yield (87%) and TMS-protected acetylene was used as a model alkyne.

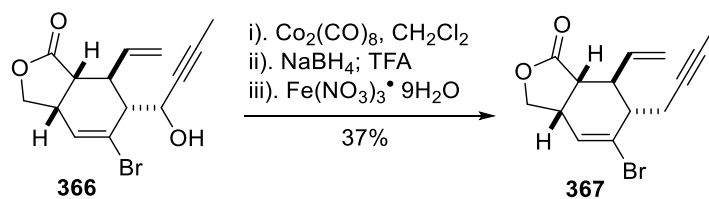


Scheme 95: Synthesis of iodide ent-359 and attempted conversion to alkyne 362

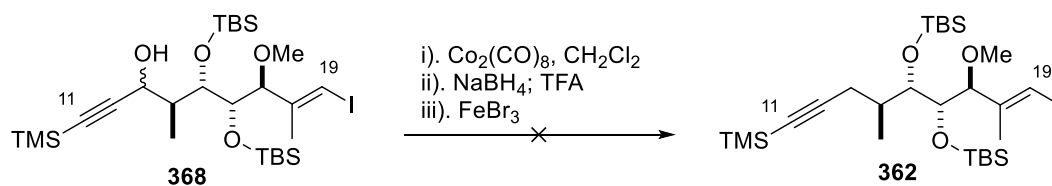
Disappointingly, none of the conditions attempted delivered the desired product. TMS-protected acetylene was lithiated with *n*-BuLi at –78 °C before addition to the iodide. No reaction was observed at



Scheme 96: Proposed C_{12} - C_{13} bond formation via an acetylide addition into aldehyde **363**



Scheme 97: Nicholas type deoxygenation by Clarke and coworkers.



Scheme 98: Attempted deoxygenation via a Nicolas reaction

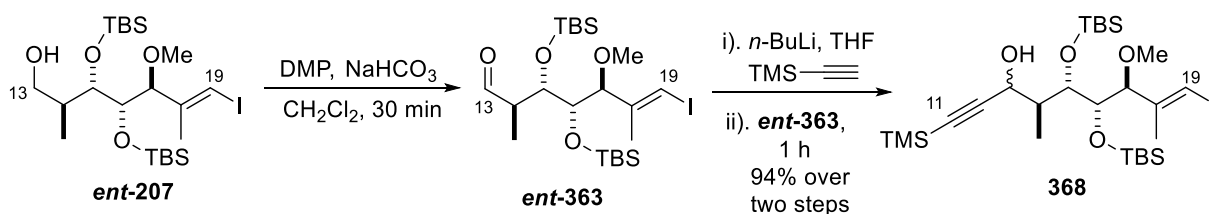
this temperature, or upon warming to 0 °C (**Table 13, entry 1**). Addition at –78 °C and immediate warming to room temperature, followed by refluxing also only returned starting material. Considering that the lithiated acetylene might be too hard a nucleophile for the relatively soft alkyl iodide, addition of the corresponding cuprate was attempted (**entry 3**), but likewise without success.

Entry	Reagent	Solvent	Temperature	Outcome
1	TMS—C≡C—Li	THF	–78 °C → 0 °C	No reaction
2	TMS—C≡C—Li	THF	–78 °C → reflux	No reaction
3	TMS—C≡C—Li, CuI	THF	–78 °C → rt	No reaction

Table 13: Attempted displacement conditions to afford alkyne **362**

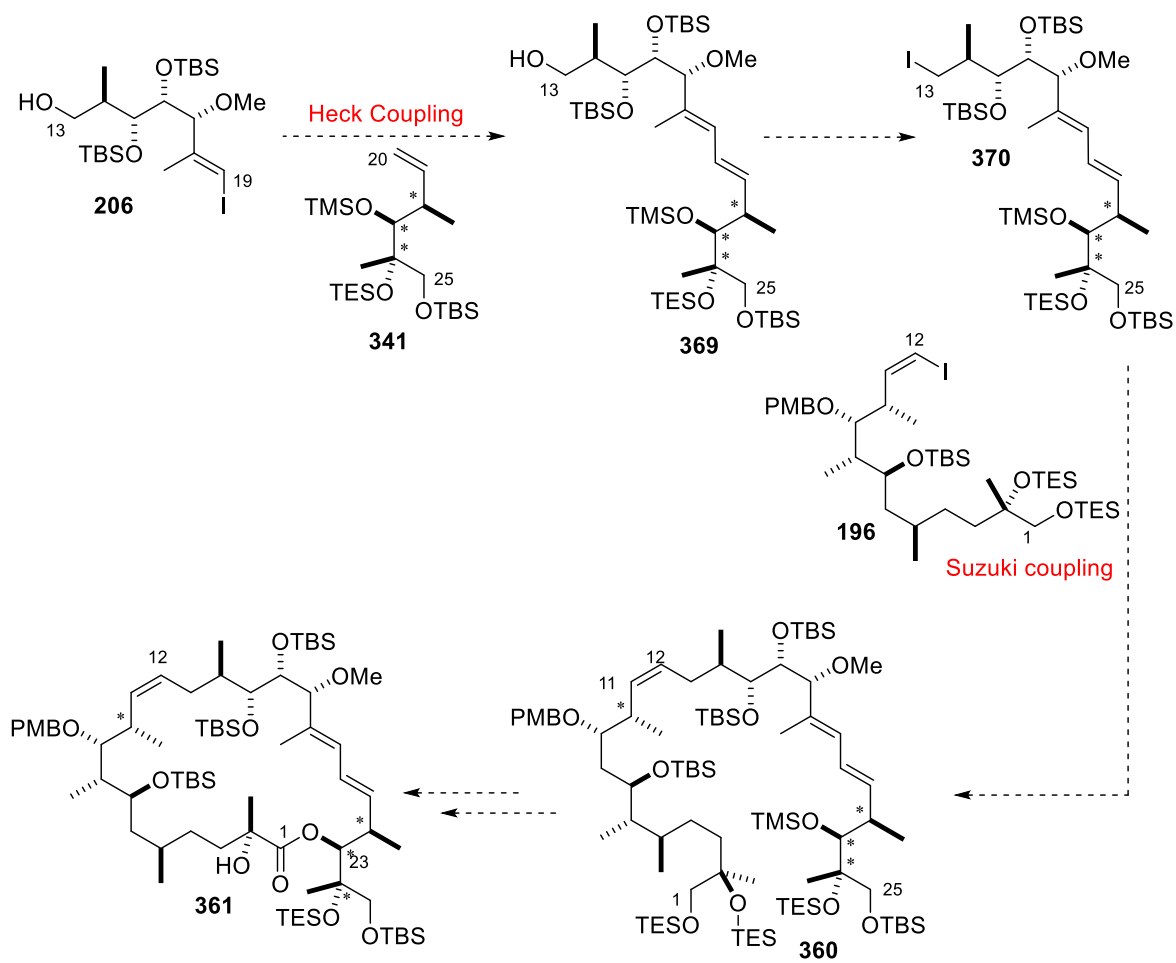
With attempts at a direct substitution proving fruitless, an alternative strategy encompassing fragment union *via* the addition of lithiated alkyne **358** into aldehyde **363** and subsequent removal of the resulting alcohol was proposed (**Scheme 96**). A Lindlar reduction should then afford the complete C₁–C₁₉ fragment **206**. As with the displacement studies, TMS-acetylene was used as a model for the C₁–C₁₂ fragment.

Accordingly, alcohol **ent-207** was oxidised with Dess-Martin periodinane in excellent yield to aldehyde **ent-363**. Deprotonation of TMS-acetylene as before, followed by addition into the aldehyde, afforded propargylic alcohol **368** as a 2.5:1 mixture of diastereomers (94% over two steps, **Scheme 99**)



Scheme 99: Oxidation of alcohol **ent-207** and subsequent acetylide addition.

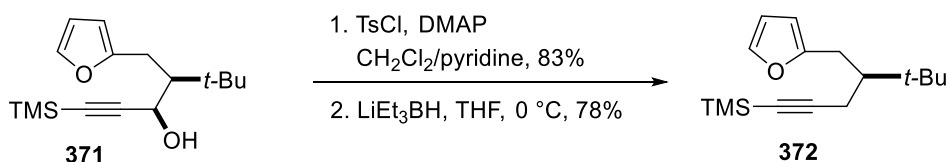
With propargylic alcohol in hand, attention turned to deoxygenation strategies. Since the vinyl iodide was deemed unlikely to survive Barton-McCombie deoxygenation conditions,¹⁴³ due to its likely reaction under a radical mediated process, alternative deoxygenation protocols were sought. Considering the alcohol requiring displacement was propargylic, it seemed pertinent to attempt to utilise this functionality. A Nicholas type deoxygenation was therefore initially considered instead.^{144–146} In 2009, Clarke and co-workers¹⁴⁷ described the deoxygenation of propargylic alcohol **366** under Nicholas conditions (**Scheme 97**). Co-ordination of the octacarbonyl dicobalt to the alkyne, with subsequent protonation of the alcohol and loss of water, gives a stabilised [(propargylium)Co₂(CO)₆]⁺ cation. Reduction out of the cation with sodium borohydride, followed by oxidative decomplexation of the cobalt



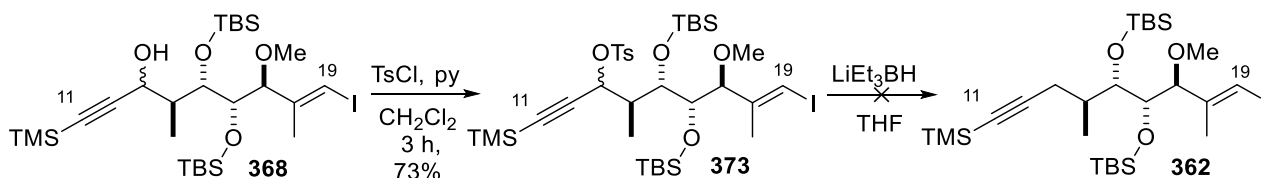
Scheme 100: Revised fragment coupling strategy

with iron (III) nitrate gave alkyne **367** in 37% yield. Attempting to use the same methodology on our system however disappointingly delivered none of the desired product (**Scheme 98**).

Alternatively, it was envisaged that the hydroxyl could be removed by conversion into a good leaving group and displacement by a hydride source. Encouraged by a paper from De Clercq,¹⁴⁸ in which he describes the tosylation of propargylic alcohol **371** under standard conditions, followed by the addition of lithium triethylborohydride (Super Hydride®) to afford alkyne **372** (**Scheme 101**), we sought to replicate this result. Diastereomeric alcohols **368** were treated with tosyl chloride and pyridine to afford tosylates **373** in 83% yield. Exposure of these tosylates to Super Hydride® unfortunately only returned starting material (**Scheme 102**). With three electron-donating groups, Super Hydride® is one of the strongest hydride sources commercially available. Considering the lack of reactivity from both these proposed methods, an alternative strategy was considered.



*Scheme 101: Reductive cleavage of propargylic alcohol **371** by De Clercq*

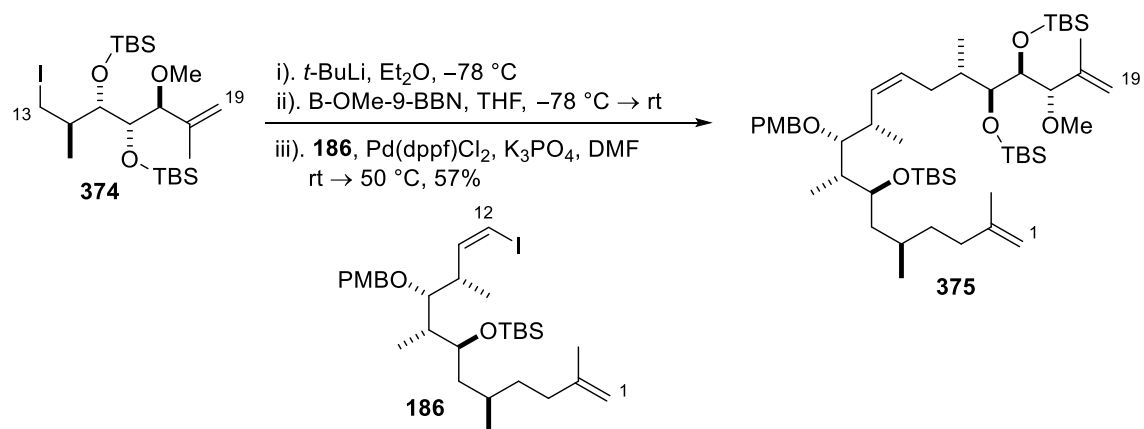


*Scheme 102: Tosylation of alcohol **368** and attempted displacement with Super Hydride®*

5.1.2 Model Studies to Investigate C₁₂-C₁₃ Suzuki Coupling

With the failure of acetylide based methods to form the C₁₂-C₁₃ bond, it became clear that the fragment union strategy would need to be revised. An initial coupling of the C₁₃-C₁₉ and C₂₀-C₂₅ fragments *via* a Heck coupling would allow for a coupling between the C₁-C₁₂ and C₁₃-C₂₅ fragments *via* a palladium-catalysed cross coupling, no longer in the presence of the C₁₉ vinyl iodide.

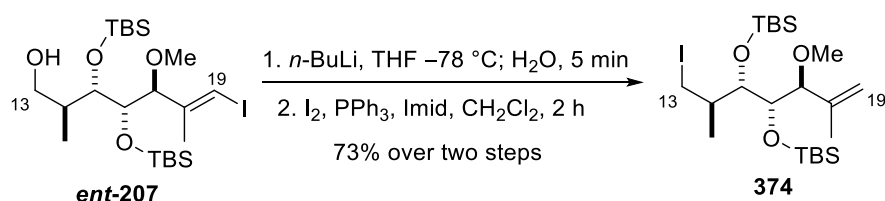
Conversion of Heck product **369** into iodide **370** would allow for a similar lithiation-borylation-Suzuki coupling sequence to that used to form the C₂-C₃ bond, as described in **Section 2.3.3**. Successful formation of the C₁₂-C₁₃ bond would furnish the complete C₁-C₂₅ fragment **360**, converging with the



Scheme 104: Model Suzuki coupling to form C₁₂-C₁₃ bond

previous fragment union strategy and amenable to macrolactonisation after a further four steps (**Scheme 100**).

To this end, a truncated fragment to model for the C₁₃-C₂₅ piece was synthesised to investigate a potential Suzuki cross coupling to construct the C₁₂-C₁₃ bond. Vinyl iodide **ent-207** was treated with *n*-BuLi at low temperature to produce the corresponding vinyl lithium species, which was then quenched with water, affording the terminal alkene. Appel conditions were then used to give iodide **374** in 73% yield over both steps (**Scheme 103**). As with other fragment coupling studies, this truncated fragment was synthesised in enantiomeric series to the natural product (in the C₁₃-C₁₉ region), due to greater availability of stocks of (*S*)-Roche ester in our laboratory.

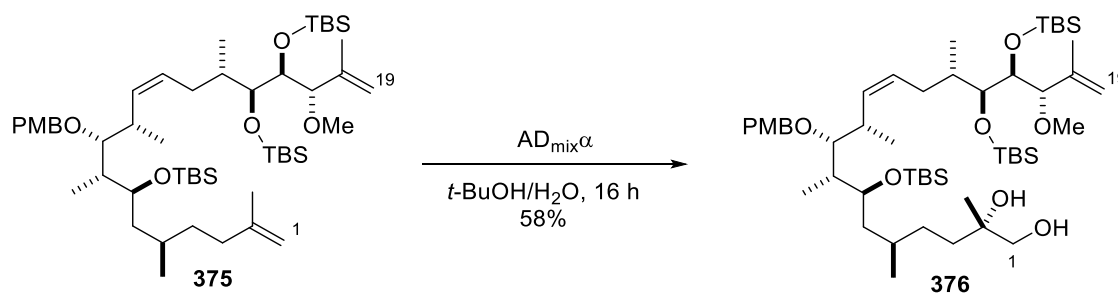


*Scheme 103: Conversion of alcohol **ent-207** into model iodide **374***

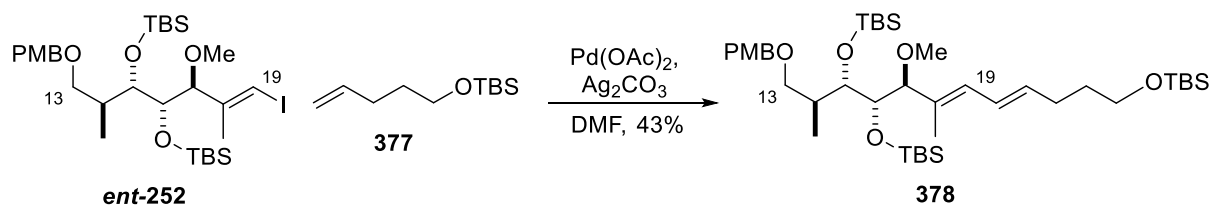
For the purposes of investigating this fragment union reaction, a slightly simplified C₁-C₁₂ fragment was also synthesised (as described in **Section 2.3.4**); functionalising the C₁₂ terminus prior to dihydroxylation across the C₁-C₂ bond. Treatment of this truncated analogue (**186**) with *t*-BuLi at low temperature afforded the alkyl lithium species, which could be swiftly trapped with OMe-9-BBN. Submission of this alkyl boronate to Suzuki coupling conditions (Pd(dppf)Cl₂, K₃PO₄, DMF) with vinyl iodide **186**, furnished the truncated C₁-C₁₉ piece. Several attempts were required to afford the product in good yield. Whereas the C₂-C₃ bond formation typically reached completion at room temperature, this reaction repeatedly stalled (or slowed down) at around 60% completion after 16 hours at rt. Pleasingly though, warming the reaction mixture to 50 °C for an additional 3 hours proceeded to push the reaction to completion affording alkene **375** in 57% yield (**Scheme 104**).

This could be attributed to the reaction being hampered by the slightly greater steric bulk around both the boronate and the vinyl iodide or the use of a vinyl iodide in place of a vinyl bromide. Buchwald reports that whilst vinyl iodides typically undergo oxidative addition at a faster rate, this process is generally no longer the rate determining step in a Suzuki coupling mechanism.¹⁴⁹ Improved ligands (such as the diphenylphosphineferrocene one used in this instance), have increased the rate of this process. Instead, the deprotonation step is typically rate-determining and this had been shown to be slower with the less acidic iodide species compared with the respective bromides or chlorides. Attempts with other ligand/base combinations, such as triphenylarsine and caesium carbonate failed to provide an improvement on the original results.

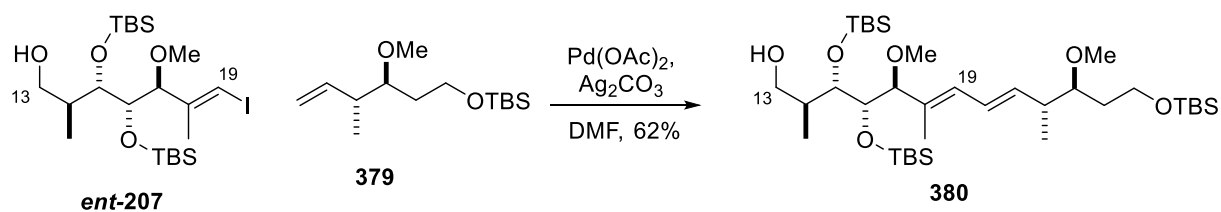
It was proposed that a late-stage dihydroxylation across the C₁-C₂ alkene immediately prior to oxidation and macrolactonisation would decrease the step count of the longest linear sequence; obviating the requirement for diol protection. It was envisaged that the C₁-C₂ olefin should react preferentially (due to its slightly higher electron density), over the 1,2-disubstituted C₁₁-C₁₂ alkene and the C₁₈-C₁₉ alkene with an allylic methoxy group, although we expected the difference to the latter to be more prominent with the full diene in place. With triene **375** in hand, a regio- and stereoselective dihydroxylation could be attempted. For these initial studies (and operational simplicity), AD_{mix}α was used as the reagent. We were encouraged by an initial result, affording the desired diol **376** in 58%, but unfortunately this result was unreproducible (**Scheme 105**). Given its unreliability, this somewhat adventurous transformation was not pursued. Instead, dihydroxylation immediately post C₂-C₃ bond formation was prioritised, followed by protection as the *bis*-TES ether.



*Scheme 105: Regioselective C₁-C₂ dihydroxylation of triene **375***



Scheme 106: Heck coupling between vinyl iodide **ent-252** and model alkene **378**



Scheme 107: Heck coupling between vinyl iodide **ent-207** and model alkene **379**

Entry	R =	Alkene, equiv.	Pd loading	Time	Outcome ^a
1	PMB	377 , 1.0	1 mol%	10 hours	20 : 50 : 30
2	PMB	377 , 1.5	1 mol%	10 hours	30 : 45 : 25
3	PMB	377 , 2.0	1 mol%	18 hours	0 : 67 : 33
4	H	379 , 1.5	1 mol%	18 hours	20 : 80 : 0
5	H	379 , 1.5	10 mol%	18 hours	62% isolated yield

a: Ratio of starting material : product : side product

Table 14: Optimisation of the C₁₉-C₂₀ Heck coupling

5.2 Formation of the C₁₉-C₂₀ Bond

5.2.1 Model Studies to Investigate C₁₉-C₂₀ Heck Coupling

With a reliable method for C₁₂-C₁₃ bond formation in place, attention turned to exploring the C₁₉-C₂₀ coupling. Taking inspiration from the Paterson synthesis of Leoidermatolide,¹⁵⁰ a Heck coupling catalysed by Pd(OAc)₂ was proposed. With the C₂₀-C₂₅ fragment synthesis still in progress, a model system was employed to investigate the reaction, initially using alkene **377** (Scheme 106).

Employing 1 mol% of Pd(OAc)₂, and 1.0 equiv. of Ag₂CO₃ in DMF and using an equimolar ratio of the vinyl iodide **ent-207** and alkene **379**, the reaction failed to reach completion. Frustratingly, both starting materials, the product and a side product impurity co-ran by TLC (Table 14, entry 1). A similar result was obtained when the equivalents of the alkene coupling partner was increased to 1.5. Prolonging the reaction time to 18 hours (entry 3) resulted in the reaction reaching completion, although the product was still produced in a 2:1 ratio with the impurity. Unable to be separated from the product, the identity of this side-product remains unknown.

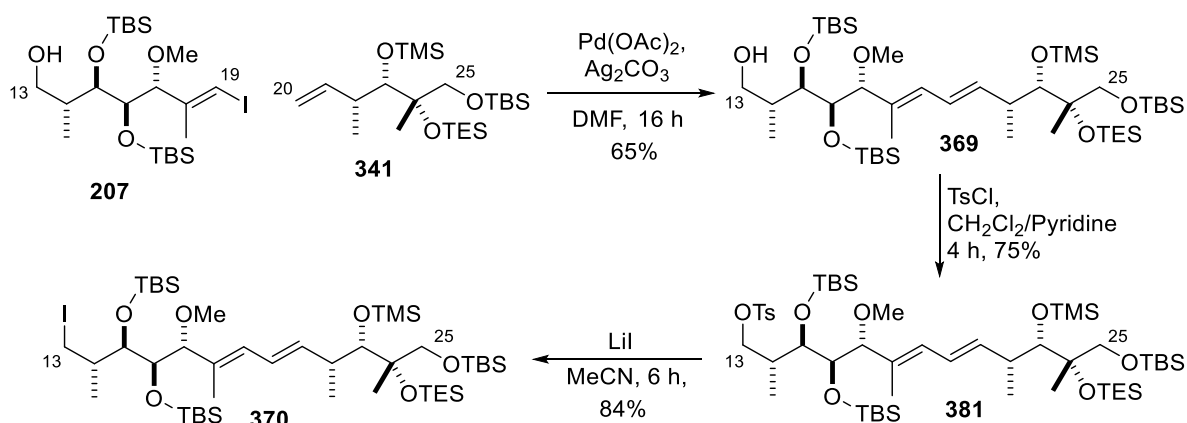
Attempted PMB deprotection of this Heck product mixture with DDQ led to considerable amounts of decomposition, indicating that the methoxydiene moiety is incompatible with these reaction conditions. Considering the amenability of cross couple reactions to free hydroxyl groups, the obvious solution appeared to be a reversal of steps. PMB deprotection proceeded very smoothly (as described in section 3.3.3), giving alcohol **ent-207** in 90% yield.

Drawing on the experience of these related studies, the proposed deprotection of the C₉ PMB ether during the endgame under the same conditions may need to be reconsidered. Alternative conditions have been reported in the literature including the use CAN and LiDBB, so these can also be attempted.

At this junction, it was considered that using a model alkene with greater similarity to the actual substrate would be sensible. To this end, the vinyl iodide was reacted with alkene **379** instead, under the same conditions (Scheme 107). Conversion was around 80%, but increasing the catalyst loading to 10 mol% afforded the desired product in 62% yield, with no production of the side product.

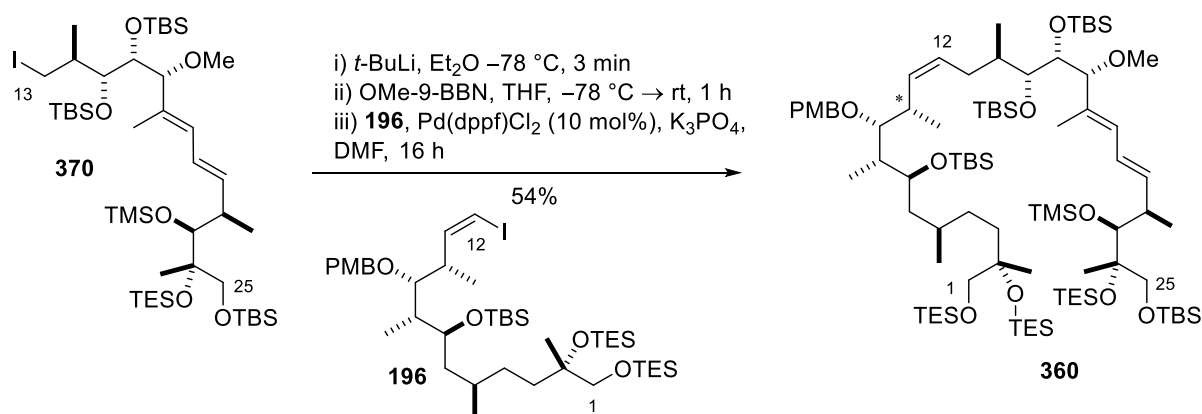
5.2.2 C₁₉-C₂₀ Heck Coupling and C₁₂-C₁₃ Suzuki Coupling to give alkene **360**

With conditions for the C₁₉-C₂₀ Heck coupling optimised on a model system, attention turned to the real fragment. Treatment of vinyl iodide **207** (now being used in the natural enantiomeric series) and alkene **341** with 10 mol% Pd(OAc)₂ and Ag₂CO₃ afforded diene **369** in 65% yield (**Scheme 108**). Attempted conversion of the model Heck coupling product to the iodide under Appel conditions led to decomposition. Instead, generation of the corresponding tosylate (**381**) proceeded smoothly, in 75% yield. Displacement with lithium iodide then gave iodide **370** in 84% yield, in preparation for C₁₂-C₁₃ bond coupling.



*Scheme 108: Heck coupling between **207** and **341** with subsequent elaboration to iodide **370***

With iodide **370** and vinyl iodide **196** in hand the Suzuki coupling to unite the C₁-C₁₂ and C₁₃-C₂₅ fragments could be attempted. Using the conditions optimised on vinyl iodide **186** and iodide **384**, alkene **360** was synthesised in 54% yield (**Scheme 109**). With limited material and a lack of time, this C₁-C₂₅ fragment represents the endpoint of the research to date. Proposals for the elaboration of this intermediate (**360**) into the truncated macrocycle can be found in **section 5.4**.



Scheme 109: Suzuki cross coupling between the C₁-C₁₂ and C₁₃-C₁₉ fragments

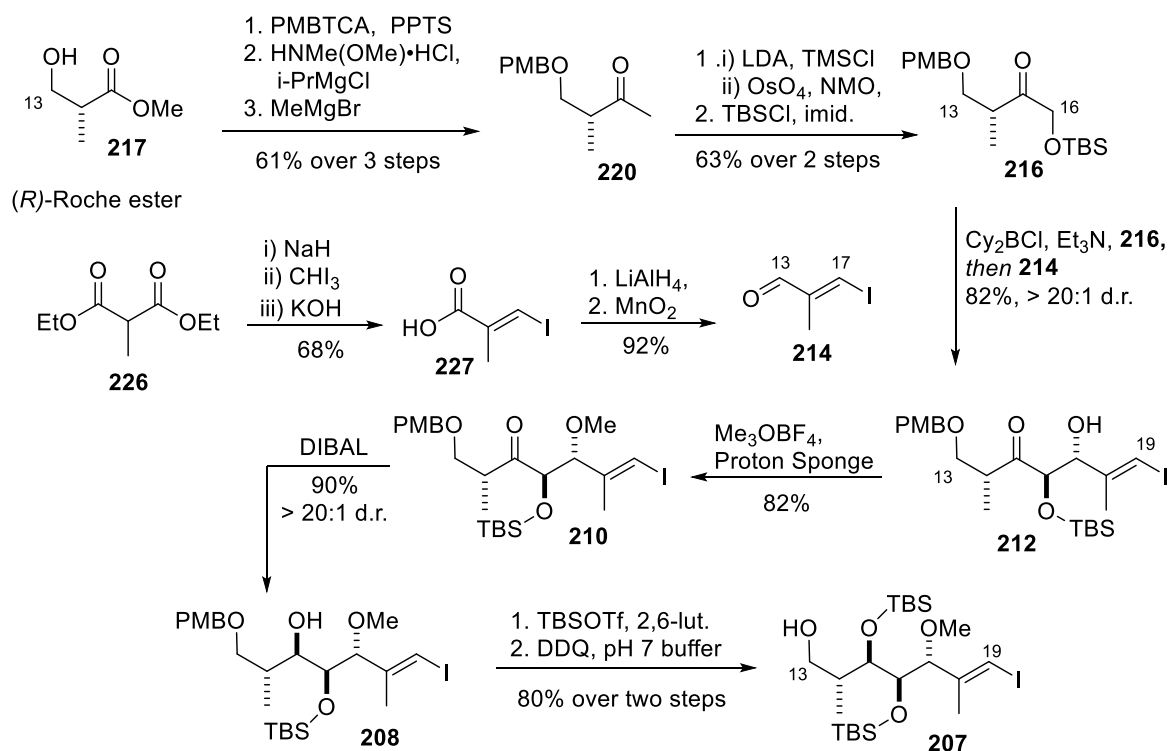


Scheme 110: Successful route to the completed C₁-C₁₂ fragment

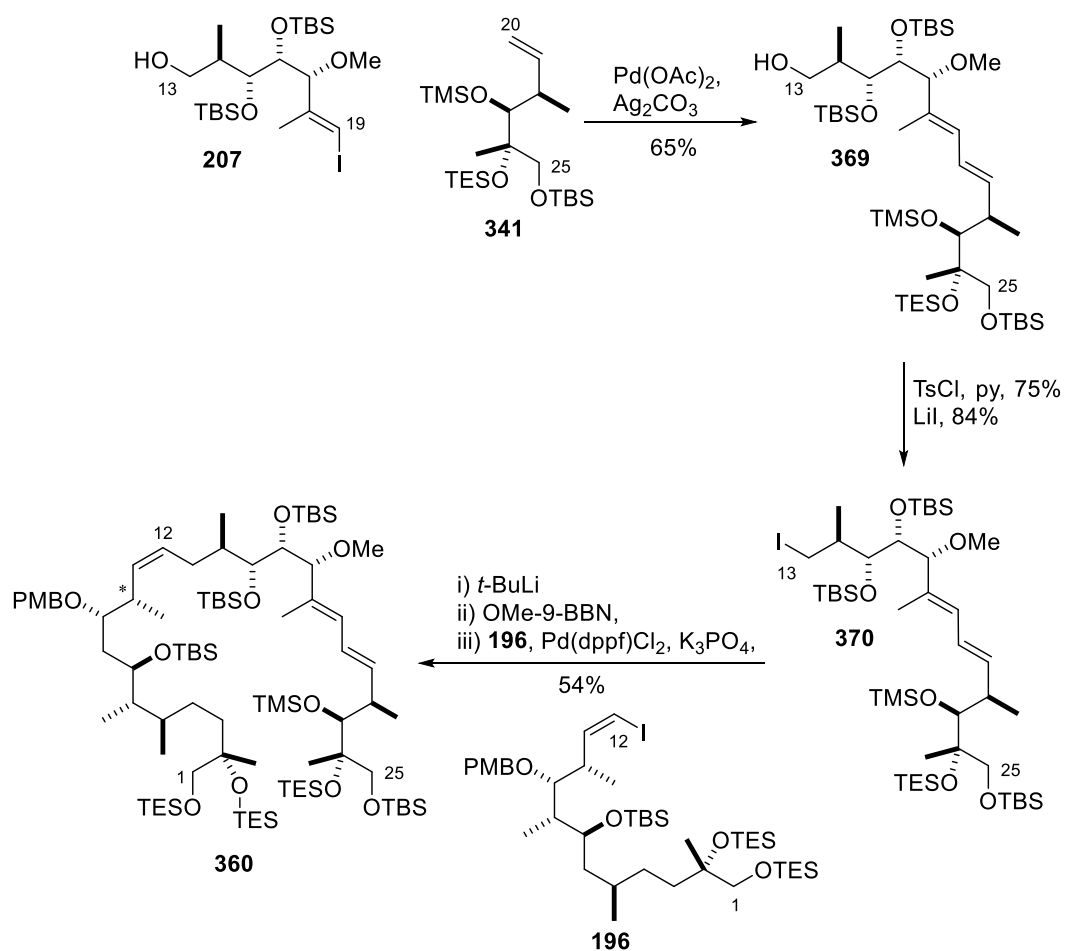
5.3 Conclusions

All three macrocycle fragments have been synthesised. The successful route to the C₁-C₁₂ fragment is detailed in **Scheme 110**. Vinyl iodide **196** had been produced in 17 steps from diacid **124** in 4.5% overall yield. The C₅ methyl stereocentre was installed in 96% ee using an enzymatic desymmetrisation. A boron-mediated *anti* aldol with *in situ* reduction has been used to install the C₇-C₁₀ stereotetrad as a single diastereomer. The C₂-C₃ bond was constructed *via* an *in situ* Suzuki cross coupling, which was subsequently subjected to a Sharpless asymmetric dihydroxylation to install the C₂ stereocentre.

The successful route to the C₁₃-C₁₉ fragment is detailed in **Scheme 111**. Vinyl iodide **207** was synthesised in 10 steps from (*R*)-Roche ester in 15% overall yield. The C₁₄-C₁₇ stereotriad was constructed using a boron-mediated *anti* aldol, affording the aldol adduct in greater than 20:1 d.r. The C₁₅ stereocentre was then installed *via* a substrate controlled reduction of the C₁₅ ketone.

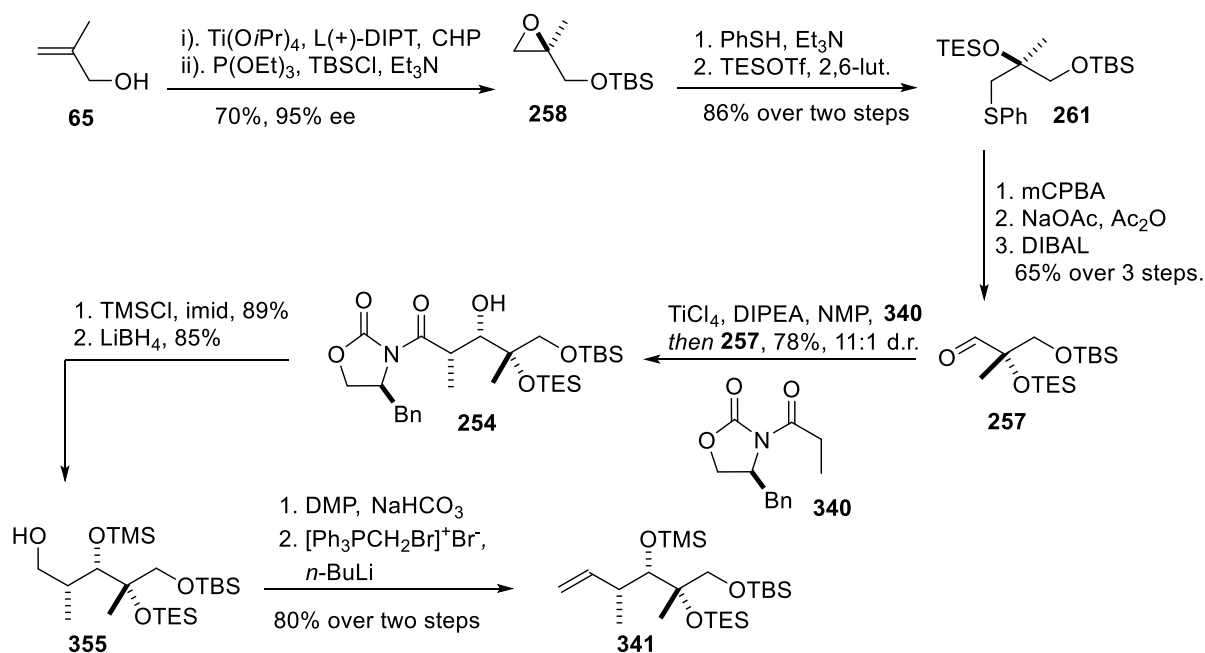


Scheme 111: Successful route to the completed C₁₃-C₁₉ fragment



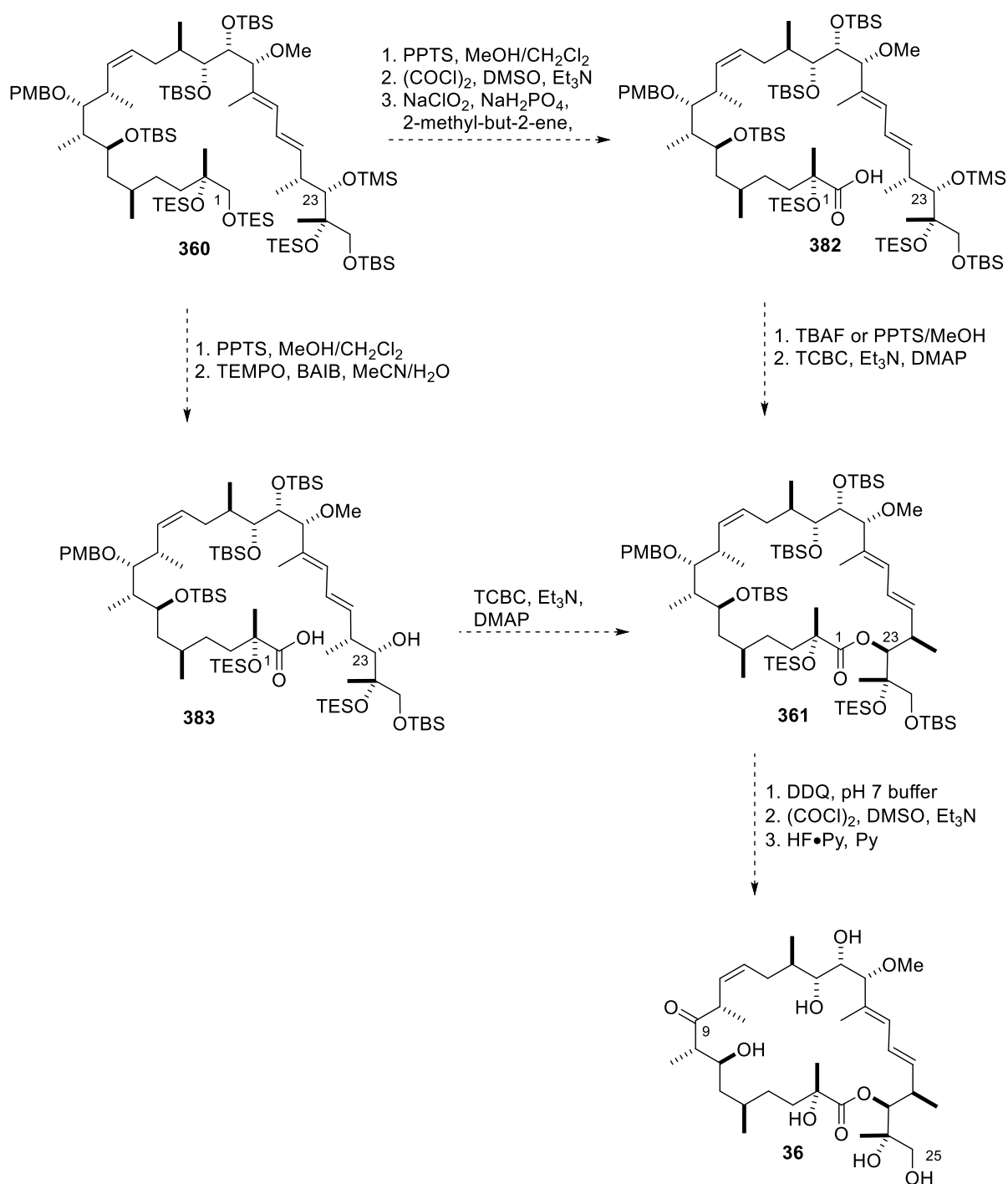
Scheme 112: Fragment union strategy to $\text{C}_1\text{-C}_{25}$ fragment

One possible stereoisomer of the C₂₀-C₂₅ fragment has been synthesised. Alkene **341** was produced in 11 steps from isobutenol in 18% overall yield (**Scheme 113**). A Sharpless asymmetric epoxidation has been used to install the C₂₄ stereocentre. An Evans aldol was then used to construct the *syn* stereochemistry of this stereoisomer. Importantly, with use of the enantiomeric tartrate catalyst for the epoxidation, the opposite enantiomer of the Evans oxazolidinone auxiliary and an *anti* aldol using a lactate derived ketone, all the other seven possible stereoisomers of this fragment are accessible.



Scheme 113: Successful route to one stereoisomer of the C₂₀-C₂₅ fragment

Investigations into an endgame strategy are well underway (**Scheme 112**). The C₁₉-C₂₀ bond has been constructed using a Heck coupling. Alcohol **369** has also been converted into the corresponding iodide **370** over two steps. This iodide then underwent a lithiation, borylation, Suzuki coupling sequence with vinyl iodide **196** to give the fully elaborated C₁-C₂₅ fragment **360**. In conclusion, whilst the synthesis has not progressed far enough to conduct structural determination studies, almost all the chemistry required to produce the truncated macrocycle has been developed. Proposed routes for the conversion of the C₁-C₂₅ fragment into the truncated macrocycle (**36**) for NMR studies are detailed in **section 5.4**.



Scheme 114: Proposed route from TES ether **360** to the truncated macrocycle **36**

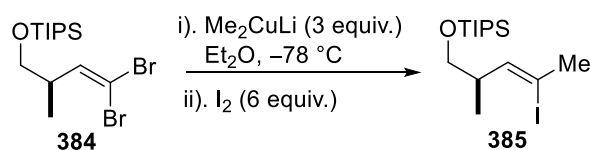
5.4 Future Work

The proposed route from C₁-C₂₅ fragment **360** will proceed *via* site-selective deprotection of the C₁ TES ether, with PPTS in MeOH/CH₂Cl₂ (**Scheme 114**). Double oxidation of the ensuing primary alcohol under Swern (oxalyl chloride, DMSO, Triethylamine) and Pinnick (NaClO₂, NaH₂PO₄, 2-methyl-but-2-ene) conditions should afford the corresponding carboxylic acid **382**. We propose that the next most labile silyl ether, would be the TMS ether at C₂₃. Deprotection with PPTS/MeOH or TBAF should afford the secondary alcohol in preparation for a Yamaguchi macrolactonisation to give macrolactone **361**. In the instance that site selective deprotection of the C₁ TES ether in the presence of the C₂₃ TMS ether is not possible, numerous methods have been reported in the literature for the chemoselective oxidation of a primary alcohol in the presence of a secondary alcohol.^{151–153} Therefore simultaneous deprotection of both silyl ethers should not be problematic.

Orthogonal protection of the C₉ alcohol should allow for selective deprotection and oxidation to install the C₉ ketone. As discussed in **section 5.2.1** though, deprotection of the C₉ PMB ether in the presence of the C₁₈-C₂₁ diene might be a challenging step. Oxidative cleavage of the PMB ether with DDQ or LiDBB should hopefully deliver the secondary alcohol smoothly. Oxidation of the C₉ alcohol to the ketone could take place under Swern or Dess Martin oxidation conditions. A global deprotection of the remaining silyl protecting groups with HF/pyridine should then give the truncated macrocycle **36** in preparation for NMR comparison with the natural product.

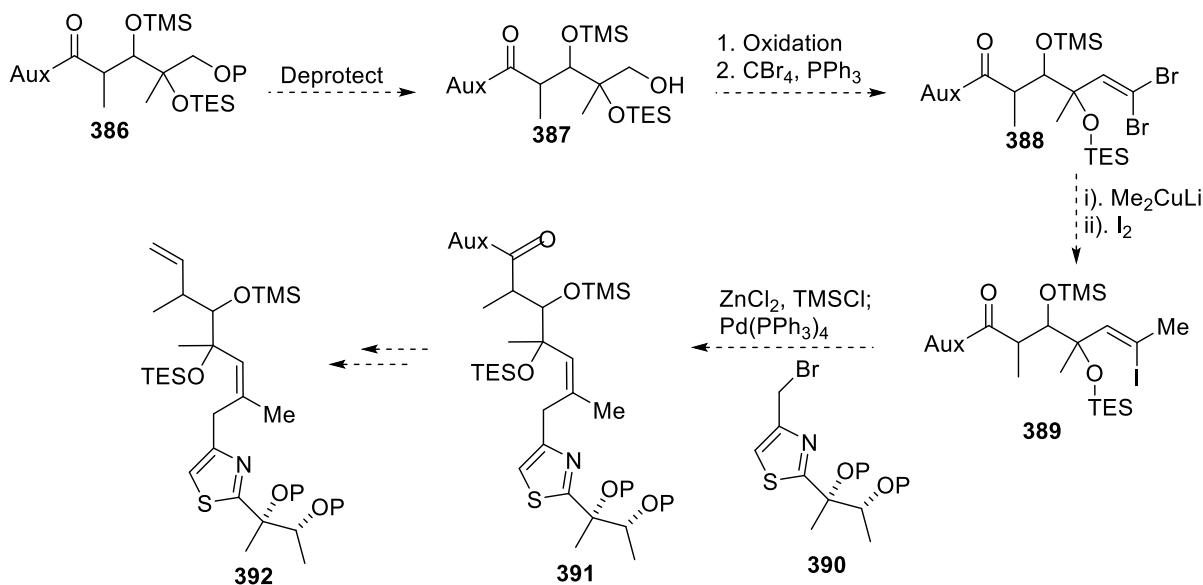
It is hoped that the two side chains will have only minimal effect on the NMR shifts and coupling constants of the macrocycle environments. Thus, comparison of the NMRs of truncate **36** to the natural product NMRs (provided by Moore and Yoshida) should provide a good indication of the most likely configuration of the three stereocentres lying within the macrocycle; specifically, those at C₁₀, C₂₂ and C₂₃. With confidence in these stereocentres a partial synthesis of the C₂₃-C₃₂ side chain will be carried out to explore permutations of the C₂₄ stereocentre. Analysis of both ¹H and ¹³C chemical shifts as well as ¹H-¹H coupling constants should hopefully indicate the likely stereochemistry of the natural product. It is also proposed that the proximity of three of the unknown stereocentres to the C₂₃ alcohol may aid the structural determination, with one or more of the stereoisomers proving too crowded for the macrocycle to form.

If NMR comparison at the macrocycle stage has provided confidence in a single stereoisomer of the C₂₀-C₂₅ fragment, it is proposed that a modified strategy could be used to complete the natural product. A more convergent approach will incorporate the thiazole side chain prior to macrolactone fragment union, taking into account the number of steps required for the C₁-C₁₂ fragment. Deprotection of the C₂₅ alcohol immediately post Evans or lactate-derived aldol and subsequent oxidation and submission to Corey-Fuchs olefination conditions should give vinyl dibromide **388**. Installation of the C₂₆ methyl group and conversion to the (*Z*)-vinyl iodide takes inspiration from work by Miyashita,¹⁵⁴ in which Roche ester derived vinyl dibromide **384** is transformed into the requisite vinyl iodide **385** by the addition of Me₂CuLi and trapping out of the ensuing vinyl copper species with iodide (**Scheme 115**)

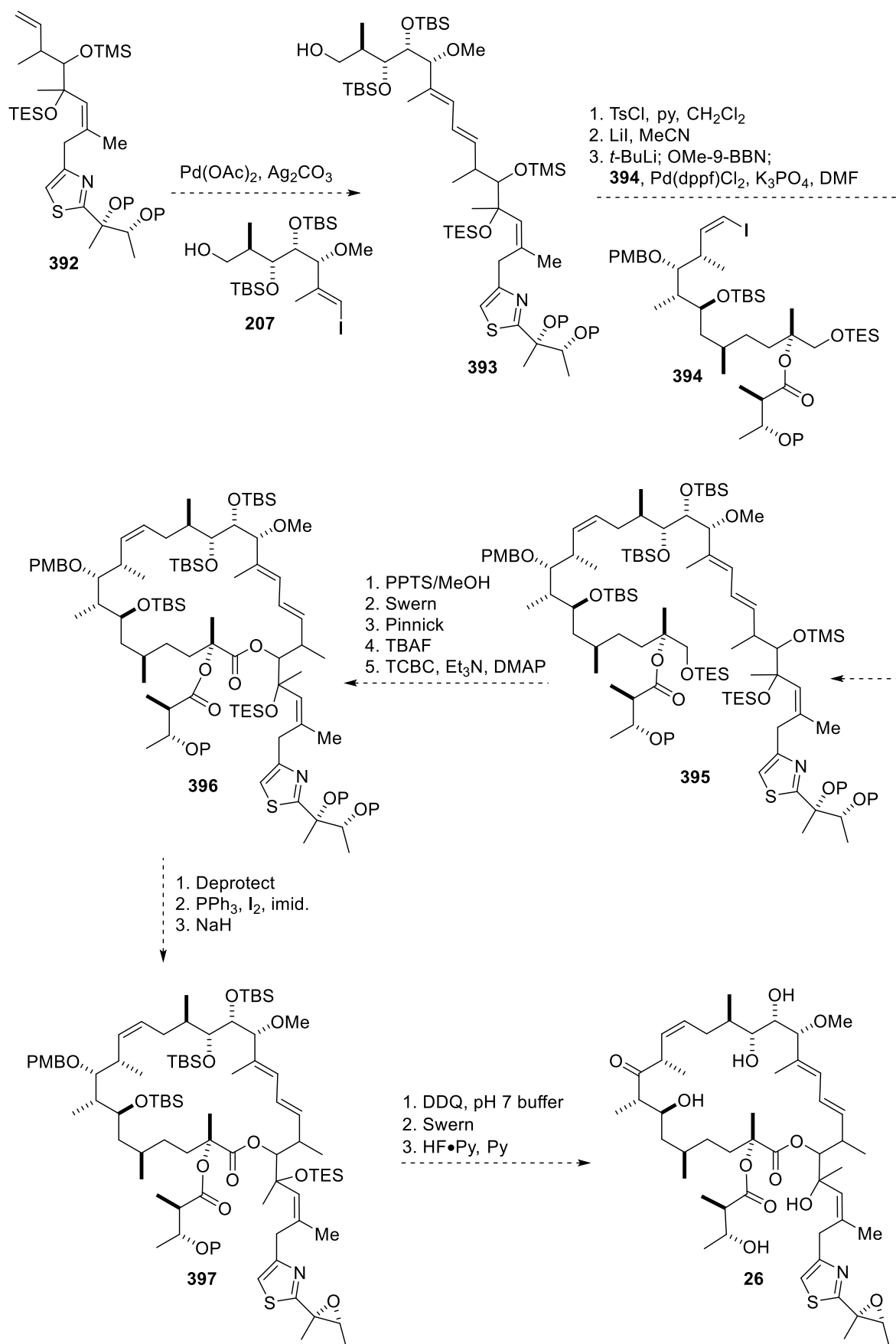


*Scheme 115: Precedent for the formation of a (*Z*)-vinyl iodide from vinyl dibromide **384***

With vinyl iodide **389** in place, we envisage a Negishi cross coupling to the thiazole side chain **390**. The corresponding iodide has been synthesised by Bing Yuan Han¹⁵⁵ in the Paterson lab, but was found to be light-sensitive, so a modification to the bromide should hopefully provide a solution to these issues. The sensitive epoxide moiety will be maintained as the protected diol until the final stages of the endgame. Coupled product **391** could then be converted into the completed C₂₁-C₃₂ fragment in 3 steps beginning with cleavage of the benzoate or Evans auxiliary (**Scheme 116**).



Scheme 116: Proposed route to completed C₂₀-C₃₂ fragment incorporating the thiazole moiety prior to macrolactonisation



Scheme 117: Proposed endgame to patellazole B

With the C₂₁-C₃₂ fragment in hand, Heck coupling with the C₁₃-C₁₉ fragment under the previously optimised conditions should provide alcohol **393**, which can then be converted into the corresponding iodide. Suzuki coupling with a modified C₁-C₁₂ fragment **394** (with the ester-linked side chain already in place) should then afford the complete C₁-C₃₂ linear fragment. At this point, the route converges with the route proposed to furnish the simplified macrocycle. Selective deprotection of the C₁ primary TES, will precede double oxidation under Swern and Pinnick conditions, deprotection of the C₂₃ TMS and a Yamaguchi macrolactonisation to give lactone **396**.

Deprotection of the C₃₁-C₃₂ diol and conversion of the secondary alcohol to the corresponding iodide under Appel conditions will proceed with inversion of configuration. Deprotonation of the tertiary alcohol should then displace the iodide, affording epoxide **397**. Deprotection of the C₉ PMB ether with DDQ or LiDBB and subsequent oxidation should reveal the ketone moiety. A final global deprotection of the remaining silyl groups with HF·py should then afford patellazole B (**Scheme 117**).

Chapter 6: Experimental

6.1 General Comments

Materials: All reagents, obtained from Acros, Aldrich, Alfa Aesar, Fluka, Fluorochem and Lancaster fine chemicals suppliers, were used directly as supplied or purified by the methods described by Armarego and Chai¹⁵⁶ except where otherwise noted in the experimental text. All non-aqueous reactions were performed in oven-dried apparatus under argon or nitrogen atmospheres, using distilled anhydrous solvents, at rt unless otherwise indicated. CH₂Cl₂, acetonitrile and methanol were distilled from calcium hydride and stored under an argon atmosphere. THF was distilled from potassium wire/benzophenone ketyl radical under an argon atmosphere. Et₂O was distilled from sodium wire/benzophenone ketyl radical under an argon atmosphere.

2,6-lutidine, Et₃N, DIPA and DIPEA were distilled from calcium hydride or calcium chloride and stored under an argon atmosphere. DMSO and DMF were distilled from MgSO₄ and stored over 4Å MS. DDQ was recrystallised from chloroform and proton sponge recrystallised from EtOH. TFA and oxalyl chloride were distilled. All solvents used in extraction and chromatography were distilled. The use of ammonium chloride (NH₄Cl), sodium bicarbonate (NaHCO₃), sodium thiosulfate (Na₂S₂O₃), brine (NaCl) and sodium / potassium (Na / K) tartrate refers to saturated aqueous solutions unless otherwise stated. 4Å MS were activated by heating under high vacuum or in a microwave. Ba(OH)₂ was prepared by heating Ba(OH)₂·8H₂O at 150 °C overnight under high vacuum before being stored in a glove box.

6.2 Analytical Procedures

Flash column chromatography was performed according to the method described by Still, Kahn and Mitra,¹⁵⁷ using a positive solvent pressure, with silica gel obtained from Merck Kieselgel 60 (230-400 mesh).

Reactions were monitored by TLC using pre-coated glass-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254). Spots were visualised by quenching of UV fluorescence and staining with potassium permanganate or phosphomolybdic acid / Ce₂(SO₄)₃, ninhydrin, anisaldehyde or vanillin dips.

NMR spectra were recorded using an internal deuterium lock for the residual protons in CDCl₃ (δ_H 7.26) at ambient probe temperatures on the following instruments: Bruker AVANCE BB 500, AVANCE TCI

cryoprobe (500 MHz) or AVANCE DRX 400 (400 MHz). Proton data are presented in the following way: chemical shift (in ppm on a δ -scale relative to $\delta_{\text{TMS}} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad, app = apparent), coupling constants (J / Hz) and assignment. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, 2D NMR experiments, or by analogy to fully interpreted spectra for structurally related compounds. Protons of OH groups are missing in some spectra due to proton exchange. ^{13}C spectra were recorded by broadband proton spin decoupling, at ambient probe temperatures on the following instruments: Bruker AVANCE BB 500 and AVANCE TCI 500 (125.7 MHz), using an internal deuterium lock for CDCl_3 ($\delta_{\text{c}} 77.0$). Chemical shifts are given in ppm on a δ -scale relative to $\delta_{\text{TMS}} = 0$. Signals are assigned according to the numbering scheme for patellazole B (**Figure 1**), unless otherwise indicated. Signals for non-patellazole related compounds are denoted by a prime, e.g. H-1'. Optical rotations were recorded on a Perkin Elmer 241 polarimeter at the sodium D-line (589 nm) using a 10 cm path length cell and are reported as follows: $[\alpha]_{\text{D}}^{20}$ concentration (c in g / 100 mL) and solvent.

High and low resolution mass spectra were recorded by the EPSRC Mass Spectrometry facility (Swansea, UK), using chemical ionisation (CI), electron impact (EI) or electron spray ionisation (ESI) techniques. The parent ion $[\text{M}]^+$, $[\text{M}+\text{H}]^+$, $[\text{M}-\text{H}]^+$, $[\text{M}+\text{NH}_4]^+$ or $[\text{M}+\text{Na}]^+$ is quoted. High resolution values are calculated to 4 decimal places from the molecular formula.

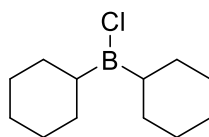
HPLC analysis was carried out on an Agilent 1200 series running in normal phase under UV detection using a ZO2RBAX RX-SIL (150 mm x 4.6 mm ID) as the analytical column. Chiral analysis was carried out using a DAICEL CHIRALPAK-IA, IB, IC (250 mm x 4.6 mm ID).

Fourier transform IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer with the sample being prepared as a thin film on a universal ATR sampling accessory. Wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1} . Only selected, characteristic IR absorption data are provided for each compound.

GC analysis was performed using a 6890N Network GC system (Agilent Technologies Inc., Palo Alto, CA, USA), equipped with a Varian CP7502, CHIRASIL DEX CB (25.0 m x 250 μm x 0.25 μL nominal) capillary column. The GC analyses were carried out in split mode (ratio 50:1) using helium as a carrier gas at a flow rate of 134 mL min^{-1} 25.00 psi. The injection port temperature was 250 $^{\circ}\text{C}$, using H_2 flow at 40.00 mL min^{-1} , air at 450 mL min^{-1} and helium makeup flow at 45.0 mL min^{-1} .

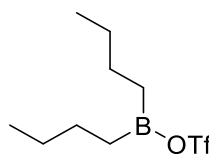
6.3 Preparation of Reagents

Dicyclohexylboron chloride



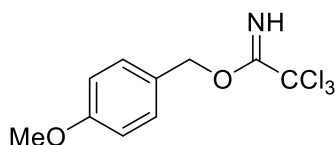
To a solution of freshly distilled cyclohexene (40.0 mL, 400 mmol, 2.0 equiv.) in Et₂O (250 mL) at –10 °C was added chloroborane dimethylsulfide complex (20.6 mL, 200 mmol, 1.0 equiv.) dropwise over 30 mins. The rate of addition was limited to control the exotherm generated. The reaction mixture was allowed to warm to 0 °C and stirred for 1 hour, then warmed to rt and stirred for a further hour. The solvent was removed by distillation at atmospheric pressure and then distillation under reduced pressure gave the reagent as a colourless liquid, b.p. 96 °C @ 0.3 mmHg.

Dibutylboron trifluoromethanesulfonate (*n*-Bu₂BOTf)



In a strictly moisture excluded environment, fresh trifluoromethanesulfonic acid (5.0 g, 33.3 mmol, 1.9 equiv.) was added dropwise over 15 min to tributylborane (8.5 mL, 34.9 mmol, 1.05 equiv.) while vigorous stirring and a cold water bath were used to control the exotherm observed. Following the addition of the tributylborane, the mixture was stirred at 0 °C for 30 min then warmed to rt and stirred for a further 1 h. Direct distillation under reduced pressure (39 °C, 0.05 mmHg) yield dibutylboron trifluoromethanesulfonate as a colourless liquid.

para-Methoxybenzyl trichloroacetimidate



To a stirring solution of KOH (150 mg, 3.13 mol, 12.1 equiv.), *para*-methoxybenzyl alcohol (35.4 g, 256 mmol, 1.0 equiv.) and tetra-*n*-butylammonium hydrogensulfate (870 mg, 2.56

mmol, 0.1 equiv.) in CH_2Cl_2 (300 mL) and H_2O (300 mL) at $-10\text{ }^\circ\text{C}$ was added trichloroacetonitrile (29.6 mL, 294 mmol, 1.15 equiv.) dropwise over 30 mins. The reaction mixture was allowed to warm to rt over 30 mins and then stirred for a further 90 mins. The layers were then separated and the aqueous layer was extracted with Et_2O (3 x 300 mL). Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (Al_2O_3) to give the title compound as a colourless liquid (50.1 g, 77%).

***i*-Propylmagnesium chloride solution**



To a suspension of magnesium turnings (12.5 g, 520 mmol, 1.1 equiv.) and iodine (5 pellets) in Et_2O (155 mL) was added 2-chloropropane (40.1 mL, 473 mmol, 1.0 equiv.) dropwise. When the addition was complete, the reaction mixture was refluxed for a further 45 min before cooling to rt to give the *i*-propylmagnesium chloride as a dark grey solution (approx. 3 M in Et_2O , 473 mmol).

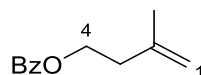
Ethylmagnesium bromide solution

To a suspension of magnesium turnings (1.11 g, 46.2 mmol, 1.1 equiv.) and iodine (1 pellet) in Et_2O (42 mL) was added bromoethane (3.14 mL, 42.0 mmol, 1.0 equiv.) dropwise. When the addition was complete, the reaction mixture was refluxed for a further 45 min before cooling to rt to give the ethylmagnesium bromide as a dark grey solution (approx. 1 M in Et_2O , 42 mmol).

6.4 Experimental Procedures

6.4.1 Preparation of the C₁-C₁₂ Vinyl Iodide

3-Methylbut-3-en-1-yl benzoate (**51**)

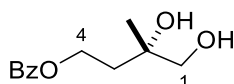


To a solution of 3-methyl-but-3-en-1-ol (2.54 mL, 25.0 mmol, 1.0 equiv.) in CH₂Cl₂ (35 mL) at 0 °C were added benzoic anhydride (7.90 g, 35.0 mmol, 1.4 equiv.) and Et₃N (7.04 mL, 50.0 mmol, 2.0 equiv.) The reaction mixture was stirred at rt for 4 h. Further CH₂Cl₂ (10 mL) was added and the reaction quenched with HCl (10% aq, 2 x 30 mL). The layers were separated and the aqueous extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were washed with NaHCO₃ (30 mL) and brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (3.90 g, 82 %).

R_f 0.35 (8:1 PE/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ_H 8.06 (2H, d, *J* = 7.3 Hz, H-Ar), 7.57 (1H, t, *J* = 7.3 Hz, H-Ar), 7.45 (2H, t, *J* = 7.3 Hz, H-Ar), 4.84 (1H, s, H-1a), 4.81 (1H, s, H-1b), 4.44 (2H, t, *J* = 6.7 Hz, H-4), 2.48 (2H, t, *J* = 6.7 Hz, H-3), 1.40 (3H, s, Me-2); ¹³C NMR (100 MHz, CDCl₃) δ_C 116.6, 141.7, 132.9, 130.3, 129.6, 128.4, 112.5, 63.1, 36.8, 22.6.

Data in agreement with literature values.¹⁵⁸

(*R*)-3,4-Dihydroxy-3-methylbutyl benzoate (**56**)

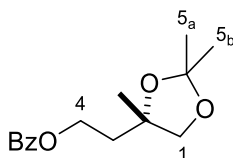


To a stirred solution of K₂OsO₂(OH)₄ (0.2 mg, 0.00052 mmol, 0.002 equiv.), (DHQ)₂AQN (2.2 mg, 0.0026 mmol, 0.01 equiv.), K₂CO₃ (107 mg, 0.78 mmol, 3.0 equiv.) and K₃Fe(CN)₆ (255 mg, 0.78 mmol, 3.0 equiv.) in ^tBuOH/water (1:1, 3 mL) was added alkene **51** (50.0 mg, 0.26 mmol, 1.0 equiv.) and the reaction mixture stirred at -7 °C for 16 h. The reaction was quenched with Na₂S₂O₃ (5 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 x 5 mL). Combined organic layers were washed with NaOH (2 M, 2 x 10 mL), dried over MgSO₄ and the solvent removed *in vacuo*. The crude

material was purified by flash column chromatography (4:1 → 1:2 PE/EtOAc) to give the title compound as a pale-yellow oil (55 mg, 93% yield, 86 ee%)

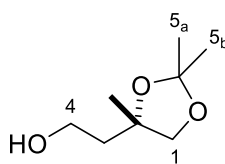
R_f 0.16 (1:2 PE/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 8.00 (2H, dd, $J = 8.3$ Hz, 1.2 Hz, H-Ar), 7.53 (1H, tt, $J = 7.3$, 1.2 Hz, H-Ar), 7.41 (2H, t, $J = 7.9$ Hz, H-Ar), 4.49 (2H, t, $J = 7.05$ Hz, H-4), 3.54 (1H, dd, $J = 11.2$, 5.1 Hz, H-1a), 3.48 (1H, dd, $J = 11.2$, 5.1 Hz, H-1b), 2.96 (1H, t, $J = 5.1$ Hz, H-3a), 2.93 (1H, s, OH), 2.07 - 2.01 (1H, m, H-3b), 1.26 (3H, s, Me-2). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_C 166.8, 133.1, 130.1, 129.5, 128.5, 72.1, 69.9, 61.6, 37.0, 23.7; (CHIRALPAK IA, 14 mL/min, 10% IPA/hexanes, R_t 13.18 min, 13.86 min (major). Data in agreement with literature values.¹⁵⁹

(S)-2-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)ethyl benzoate (49)



To a solution of **56** (73.0 mg, 0.45 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added 2,2-dimethoxypropane (1.09 mL, 8.93 mmol, 20 equiv.) and PPTS (22.6 mg, 0.09 mmol, 0.2 equiv.) and the reaction stirred at rt for 60 min. The reaction mixture was quenched with NaHCO_3 (5 mL), the layers separated and aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layers were dried over MgSO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (4:1 PE/EtOAc) to give the title compound as a pale yellow oil (78.1 mg, 99%)

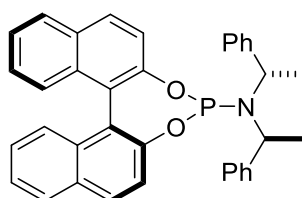
R_f 0.28 (3:1 PE/EtOAc); $[\alpha]_D^{20} + 3.48$ (c 1.00, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2984, 1720, 1602, 1453, 1379, 1316, 1275, 1115, 1071, 1029, 972, 820, 716, 680; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 8.01 (2H, d, $J = 7.5$ Hz, H-Ar), 7.53 (1H, t, $J = 7.5$ Hz, H-Ar), 7.41 (2H, t, $J = 7.5$ Hz, H-Ar), 4.51-4.38 (2H, m, H-4), 3.90 (1H, d, $J = 8.4$ Hz, H-1a), 3.75 (1H, d, $J = 8.4$ Hz, H-1b), 2.06-2.02 (2H, m, H-3), 1.39 (6H, s, H-5a, H-5b), 1.36 (3H, s, Me-2); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_C 166.3, 132.3, 130.2, 129.4, 128.3, 109.2, 79.6, 74.3, 61.5, 38.3, 27.0, 24.9; HRMS (ES+): calc. for $\text{C}_{15}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$ 265.1434, found 265.1435.

(R)-2-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)ethan-1-ol (61)

To a solution of **49** (200 mg, 0.76 mmol, 1.0 equiv.) in MeOH (8 mL) was added K_2CO_3 (261 mg, 1.89 mmol, 2.5 equiv.) and stirred at rt for 2 h. The reaction mixture was quenched with $NaHCO_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 6 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3:1 PE_{30-40}/Et_2O) to give the title compound as a colourless oil (106 mg, 88 %).

R_f 0.21 (3:1 $PE/EtOAc$); 1H NMR (500 MHz, $CDCl_3$): δ_H 3.91-3.86 (1H, m, H-4a), 3.84 (1H, d, J = 8.5 Hz, H-1), 3.78-3.73 (1H, m, H-4b), 3.77 (1H, d, J = 8.5 Hz, H-1), 1.94-1.89 (1H, m, H-3a), 1.76-1.71 (1H, m, H-3b), 1.42 (3H, s, H-5a), 1.41 (3H, s, H-5b), 1.34 (3H, s, Me-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 109.4, 81.2, 74.5, 59.3, 41.0, 27.0, 26.8, 24.9.

Data in agreement with literature values.¹⁶⁰

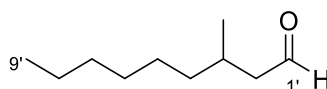
(11bS)-N,N-Bis((S)-1-phenylethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (58)

To a stirred mixture of Et_3Npph_3 (0.31 mL, 2.22 mmol, 5.0 equiv.) and PCl_3 (39 μ L, 0.44 mmol, 1.0 equiv.) at 0 °C was added a solution of Bis-[(S)-1-phenylethyl]amine (100 μ L, 0.44 mmol, 1.0 equiv.) in THF (0.5 mL). The reaction mixture was stirred at rt for 3 h, cooled to 0 °C and a solution of (R)-2,2'-binaphthol (127 mg, 0.44 mmol, 1.0 equiv.) in THF (1.2 mL) slowly added. The reaction mixture was then stirred for 16 h at rt, before being diluted with toluene (5 mL), filtered through a short pad of alumina and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (Al_2O_3 , Toluene) to give the title compound as an off-white solid (136 mg, 57%).

R_f 0.85 (Al₂O₃, Toluene); **¹H NMR** (500 MHz, CDCl₃): δ_H 7.94 (2H, d, *J* = 8.9 Hz, H-Ar), 7.92-7.88 (2H, m, H-Ar), 7.59 (1H, d, *J* = 8.9 Hz, H-Ar), 7.43 (1H, d, *J* = 8.9 Hz, H-Ar), 7.41-7.39 (2H, m, H-Ar), 7.30-7.24 (4H, m, H-Ar), 7.14-7.09 (1H, m, H-Ar), 4.54 – 4.45 (2H, m, CH(Ph)CH₃), 1.74 (6H, d, *J* = 7.1 Hz, CH₃); **¹³C NMR** (125 MHz, CDCl₃): δ_C 150.3, 149.8, 142.9, 132.6, 131.3, 130.5, 129.3, 128.3, 128.0, 127.9, 127.8, 127.2, 126.7, 126.1, 124.7, 122.3, 52.4, 21.7.

Data in agreement with literature values.¹⁶¹

3-Methyl-4-oxononanal (60)



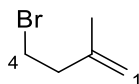
To a solution of acid-washed magnesium (232 mg, 9.60 mmol, 2.0 equiv.) and iodine (2 crystals) in Et₂O (0.5 mL) was added hexyl iodide (0.72 mL, 4.80 mmol, 1.0 equiv.) in Et₂O (4.5 mL) and gently heated to initiate Grignard reagent formation. The reaction mixture was refluxed at 45 °C for 2 h to produce a solution of hexyl magnesium iodide (0.96 M in Et₂O). To a solution of copper thiophene carboxylate (9.5 mg, 0.05 mmol, 0.05 equiv.) in CH₂Cl₂ (4 mL) was added phosphoramidite ligand **58** (23.0 mg, 0.055 mmol, 0.055 equiv.) and the solution stirred at rt for 30 min. Concurrently, crotonaldehyde (82 μL, 1.00 mmol, 1.0 equiv.), freshly distilled from CaCl₂, was added dropwise to a solution of acetyl chloride (76 μL, 1.00 mmol, 1.0 equiv.) and freshly fused ZnCl₂ (2.0 mg, 0.015 mmol, 0.015 equiv.) in CH₂Cl₂ (2 mL) at – 10 °C. The resulting solution was then added to the catalyst solution, at –78 °C. After stirring for 5 min at –78 °C, the Grignard solution (1.15 mL, 1.20 mmol, 1.2 equiv., diluted with CH₂Cl₂ (1.4 mL)) was added dropwise over 6 h *via* syringe pump. Upon completion of the addition, the reaction mixture was stirred for a further 4 h at –78 °C before being quenched with NH₄Cl (4 mL) and warmed to rt. The solution was then diluted with Et₂O and the layers separated. The aqueous layer was extracted with Et₂O (3 x 10 mL), combined organic layers dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude material, isolated as the enol acetate, was purified by flash column chromatography (80:1 PE/EtOAc). The clean enol acetate was dissolved in MeOH (10 mL) and K₂CO₃ (256 mg, 1.85 mmol, 5.0 equiv.) at rt for 1 h. The solvent was removed *in vacuo*, water (5 mL) added and the mixture extracted with Et₂O (3 x 5 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give the title compound as a colourless oil (39.0 mg, 25%).

R_f 0.32 (60:1 PE/EtOAc); **¹H NMR** (400 MHz, CDCl₃): δ_H 9.77 (1H, t, *J* = 2.4 Hz, CHO), 2.40 (1H, ddd, *J* = 15.9, 5.8, 2.2 Hz, H-2'), 2.23 (1H, ddd, *J* = 15.9, 7.9, 2.6 Hz, H-2'), 2.09-2.02 (1H, m, H-3'), 1.31-1.24 (10H,

m, H4'-8'), 0.97 (3H, d, $J = 6.8$ Hz, Me-3'), 0.89 (3H, t, $J = 1.85$ Hz, H-9'); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 203.0, 51.0, 36.8, 31.7, 29.3, 28.1, 26.8, 22.5, 19.9, 14.0.

Data in agreement with literature values.¹⁶²

4-Bromo-2-methylbut-1-ene (62)

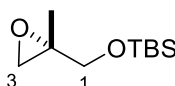


To a solution of 3-methyl-3-butene-1-ol (1.18 mL, 11.6 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at 0 °C was added PPh_3 (3.36 g, 12.8 mmol, 1.1 equiv.) followed by NBS (2.28 g, 12.8 mmol, 1.1 equiv.) in 10 portions. The reaction mixture warmed to rt and stirred for 4 h, before addition of PE (8 mL). The suspension was filtered through a short plug of silica, washed with further PE (20 mL) and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a colourless oil (533 mg, 57%).

R_f 0.28 (8:1 PE/EtOAc); ^1H NMR (400 MHz, CDCl_3): δ_{H} 4.87 (1H, s, H-1a), 4.78 (1H, s, H-1b), 3.48 (2H, t, $J = 7.4$ Hz, H-4), 2.59 (2H, t, $J = 7.4$ Hz, H-3), 1.76 (3H, s, Me-2); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 142.3, 112.6, 40.8, 30.7, 21.9.

Data in agreement with literature values.¹⁶³

(S)-tert-Butyldimethyl((2-methyloxiran-2-yl)methoxy)silane (66)



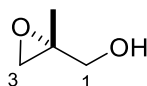
To activated powdered 3 Å MS (1.50 g), were added CH_2Cl_2 (50 mL), D-(-)-diisopropyltartrate (0.13 mL, 0.60 mmol, 0.06 equiv.) and methallyl alcohol (0.84 mL, 10.0 mmol, 1.0 equiv.) at -20 °C. After stirring for 5 min, $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.15 mL, 0.50 mmol, 0.05 equiv.) was added and the reaction mixture stirred for a further 30 min. Cumene hydroperoxide (80% in cumene, 3.60 mL, 20.0 mmol, 2.0 equiv.) was then added and the reaction flask placed in a freezer at -20 °C for 16 h. The excess peroxide was quenched with the dropwise addition of $\text{P}(\text{OEt})_3$ (2.56 mL, 15.0 mmol, 1.5 equiv.) at -20 °C over 1 h, before Et_3N (2.14 mL, 15.0 mmol, 1.5 equiv.), DMAP (60.5 mg, 0.50 mmol, 0.05 equiv.) and TBSCl (2.26 g, 15.0 mmol, 1.5 equiv.) were added and the reaction stirred for a further h at 0 °C. Upon completion, the reaction mixture was filtered through Celite®. The filtrate was then washed with tartaric acid (10% aq, 20 mL). The layers were separated and the organic layer further washed with NaHCO_3 (2 x 10 mL) and brine (2

x 10 mL), before being dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20:1 PE₃₀₋₄₀ / Et₂O) to give the title compound as a colourless oil (1.42 g, 70%).

R_f 0.25 (9:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_H 3.68 (1H, d, *J* = 11.2 Hz, H-1a), 3.62 (1H, d, *J* = 11.2 Hz, H-1b), 2.77 (1H, d, *J* = 5.0 Hz, H-3a), 2.62 (1H, d, *J* = 5.0 Hz, H-3b), 1.37 (3H, s, Me-2), 0.92 (9H, s, Si(CH₃)₃), 0.09 (3H, s, Si(CH₃)(CHb₃)), 0.08 (3H, s, Si(CH₃)(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_C 66.4, 57.0, 51.4, 25.7, 18.2, 17.9, – 5.5.

Data in agreement with literature values.¹⁶⁴

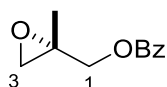
(*R*)-(2-Methyloxiran-2-yl)methanol (77)



To a suspension of activated 4Å MS (22.0 mg, 30 wt%) in CH₂Cl₂ (3.5 mL) at –30 °C were added Ti(O^{*i*}Pr)₄ (0.29 mL, 1.00 mmol, 1.0 equiv.) and D (–)-Diethyltartrate (246 mg, 1.20 mmol, 1.2 equiv.) and the reaction mixture stirred for 30 min. Methallyl alcohol (84 μL, 1.00 mmol, 1.0 equiv.) was then added and the reaction stirred for a further 30 min. *tert*-Butylhydroperoxide (5.5 M in decane, 0.55 mL, 3.00 mmol, 3.0 equiv.) was then added, stirred for 5 min and the reaction flask placed in a freezer at –20 °C for 16 h. The reaction mixture was recooled to –30 °C and quenched with a solution of FeSO₄ (2.46 g, 9.00 mmol, 9.0 equiv.) and tartaric acid (432 mg, 3.00 mmol, 3.0 equiv.) in water (2 mL) and slowly warmed to rt. The layers were separated and the organic layer washed with Na₂S₂O₃ (2 x 4 mL). The organic layer was dried over Na₂SO₄ and the solvent removed carefully *in vacuo*. The crude material was purified by flash column chromatography (2:1 PE₃₀₋₄₀/Et₂O → 100% Et₂O) to give the title compound as a colourless oil (10 mg, 11%)

R_f 0.35 (2:1 PE/EtOAc); **¹H NMR** (400 MHz, CDCl₃): δ_H 3.73 (1H, d, *J* = 12.3 Hz, H-1a), 3.61 (1H, d, *J* = 12.3 Hz, H-1b), 2.92 (1H, d, *J* = 4.8 Hz, H-3a), 2.65 (1H, d, *J* = 4.8 Hz, H-3b), 1.36 (3H, s, Me-2).

Data in agreement with literature values.¹⁶⁵

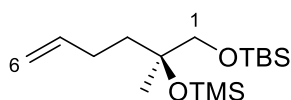
(S)-(2-Methyloxiran-2-yl)methyl benzoate**Procedure A:**

To a solution of alcohol **77** (88.0 mg, 1.00 mmol, 1.0 equiv.) in CH_2Cl_2 (8 mL) under argon at 0 °C was added benzoic anhydride (316 mg, 1.40 mmol, 1.4 equiv.) and Et_3N (0.39 mL, 2.00 mmol, 2.0 equiv.) The reaction mixture was stirred at rt for 4 h and then quenched with HCl (6 mL, 1 M aq). The layers were separated and the aqueous extracted with CH_2Cl_2 (2 x 5 mL). Combined organic layers were washed with NaHCO_3 (10 mL) and brine (10 mL) before being dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 PE/EtOAc) to give the title compound as a colourless oil (159 mg, 84 %)

Procedure B:

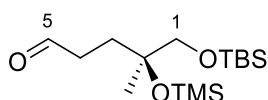
To activated powdered 3 Å MS (0.80 g), was added CH_2Cl_2 (25 mL), D (-) diisopropyl tartrate (60 µL, 0.297 mmol, 0.0595 equiv.) and methallyl alcohol (0.42 mL, 5.00 mmol, 1.0 equiv.) at -20 °C. After stirring for 5 min, $\text{Ti}(\text{O}^i\text{Pr})_4$ (74 µL, 0.25 mmol, 0.05 equiv.) was added and the reaction stirred for a further 30 min. Cumene hydroperoxide (80% in cumene, 1.8 mL, 10.0 mmol, 2.0 equiv.) was then added and the reaction placed in a freezer at -20 °C for 16 h. The excess peroxide was quenched with the portionwise addition of $\text{P}(\text{OEt})_3$ (1.28 mL, 7.50 mmol, 1.5 equiv.) at -20 °C over 1 h, before Et_3N (1.04 mL, 7.50 mmol, 1.5 equiv.) and benzoyl chloride (0.87 mL, 7.50 mmol, 1.5 equiv.) were added and the reaction mixture stirred for a further 1 h at 0 °C. The reaction mixture was then filtered through Celite® and the filtrate washed with tartaric acid (10% aq, 20 mL). The layers were separated and the organic layer washed with NaHCO_3 (2 x 10 mL) and brine (2 x 10 mL), before being dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20:1 PE/ EtOAc) to give the title compound (710 mg, 74% yield, 95% ee (CHIRALPAK IA, 14 mL/min, 0.5% IPA/hexanes, Rt 9.30 min (major), 10.06 min).

R_f 0.35 (2:1 PE/Et₂O); $[\alpha]_D^{20} + 18.4$ (c 1.00, CHCl_3); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2989, 1720, 1602, 1451, 1270, 1115, 1071, 1027, 979, 815, 710, 687; **HRMS** (ES⁺): calc. for $\text{C}_{11}\text{H}_{12}\text{O}_3$ $[\text{M}+\text{H}]^+$ 193.0859, found 193.0856; **¹H NMR** (500 MHz, CDCl_3): δ_{H} 8.01 (2H, dd, $J = 8.3, 1.5$ Hz, H-Ar), 7.55 (1H, tt, $J = 7.5, 1.5$ Hz, H-Ar), 7.43 (2H, dd, $J = 8.3, 7.5$ Hz, H-Ar), 4.52 (1H, d, $J = 12.0$ Hz, H-1a), 4.24 (1H, d, $J = 12.0$ Hz, H-1b), 2.89 (1H, d, $J = 4.8$ Hz, H-3a), 2.75 (1H, d, $J = 4.8$ Hz, H-3b), 1.50 (3H, s, Me-2); **¹³C NMR** (125 MHz, CDCl_3): δ_{C} 165.9, 133.1, 129.5, 128.8, 128.3, 67.5, 54.8, 51.7, 18.4.

(S)-4-(But-3-en-1-yl)-2,2,4,7,7,8,8-heptamethyl-3,6-dioxa-2,7-disilanonane (67)

To a solution of secondary alcohol **86** (1.00 g, 4.34 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) were added imidazole (443 mg, 6.51 mmol, 1.5 equiv.), DMAP (23.9 mg, 0.22 mmol, 0.05 equiv.) and chlorotrimethylsilane (0.66 mL, 5.21 mmol, 1.2 equiv.). The reaction mixture was stirred at rt for 2 h before being quenched with NH_4Cl (20 mL). The layers were separated, the aqueous layer extracted with Et_2O (3 x 10 mL) and combined organic layers dried over MgSO_4 . The solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (25:1 PE/EtOAc) to give the title compound as a colourless oil (830 mg, 64%)

R_f 0.45 (10:1 PE/EtOAc); $[\alpha]_D^{20} + 13.2$ (c 1.00, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2956, 2931, 1642, 1472, 1250, 1100, 1026, 908, 825, 774, 752, 666; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 5.90-5.80 (1H, m, H-5), 5.04-4.91 (2H, m, H-6), 3.42 (1H, d, $J = 9.7$ Hz, H-1a), 3.33 (1H, d, $J = 9.7$ Hz, H-1b), 2.12-2.06 (2H, m, H-4), 1.63-1.57 (1H, m, H-3a), 1.53-1.45 (1H, m, H-3b), 1.19 (3H, s, Me-2), 0.90 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.11 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_C 139.4, 113.6, 76.1, 70.0, 38.3, 27.9, 25.8, 25.0, 18.2, 2.5, -5.6; HRMS (ES+): calc. for $\text{C}_{16}\text{H}_{36}\text{O}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$ 317.2327, found 317.2328.

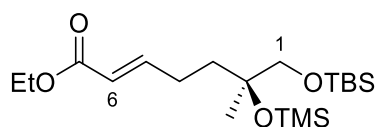
(S)-5-((tert-Butyldimethylsilyl)oxy)-4-methyl-4-((trimethylsilyl)oxy)pentanal (85)

To a solution of alkene **67** (35.0 mg, 0.11 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at -78°C was bubbled ozone until the solution turned blue. The ozone stream was then replaced with oxygen until the solution returned to colourless. The reaction mixture was quenched with PPh_3 (43.5 mg, 0.16 mmol, 1.5 equiv.) and slowly warmed to rt. The solvent was then removed *in vacuo* to give the crude product, which was purified by flash column chromatography (25:1 PE/ EtOAc) to give the title compound as a colourless oil (33.6 mg, 95%).

R_f 0.45 (10:1 PE/EtOAc); $[\alpha]_D^{20} + 18.5$ (c 1.00, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2955, 1727, 1472, 1250, 1099, 1058, 832, 775, 666, 542; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 9.75 (1H, t, $J = 2.0$ Hz, H-5), 3.41 (1H, d, $J = 9.6$ Hz, H-1a), 3.35 (1H, d, $J = 9.6$ Hz, H-1b), 2.47-2.42 (2H, m, H-4), 1.89 (1H, dt, $J = 14.1, 7.2$ Hz, H-

3a), 1.76 (1H, dt, $J = 14.1, 7.5$ Hz, H-3b), 1.22 (3H, s, Me-2), 0.90 (9H, s, $\text{SiMe}_2\text{C}(\text{CH}_3)_3$), 0.10 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 203.0, 75.6, 69.7, 38.7, 31.9, 25.7, 24.9, 18.1, 2.3, – 5.6; HRMS (ES⁺): calc. for $\text{C}_{15}\text{H}_{34}\text{O}_3\text{Si}_2$ $[\text{M}+\text{Na}]^+$ 341.1939, found 341.1937.

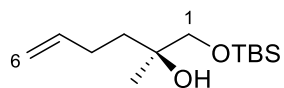
Ethyl (*S,E*)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-6-((trimethylsilyl)oxy)hept-2-enoate (68)



To a slurry of $\text{Ba}(\text{OH})_2$ (31.9 mg, 0.19 mmol, 1.8 equiv.) in THF (0.5 mL) at rt was added triethylphosphonoacetate (31 μL , 0.16 mmol, 1.5 equiv.) and the mixture stirred at rt for 45 min. A solution of aldehyde **85** (33.0 mg, 0.10 mmol, 1.0 equiv.) in THF: H_2O (40:1, 0.5 mL) was then added and the reaction mixture stirred at rt for 16 h before being quenched with NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (3 x 2 mL) and the combined organic layers were dried with MgSO_4 before the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (20:1 PE/ EtOAc) to give the title compound as a colourless oil (32.3 mg, 80%).

R_f 0.51 (4:1 PE/ EtOAc); $[\alpha]_D^{20} + 9.3$ (c 1.00, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2956, 2859, 1723, 1654, 1473, 1367, 1252, 1101, 1044, 978, 820, 776; ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.01 (1H, dt, $J = 15.7, 6.9$ Hz, H-5), 5.82 (1H, d, $J = 15.7$ Hz, H-6), 4.19 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 3.41 (1H, d, $J = 9.6$ Hz, H-1a), 3.32 (1H, d, $J = 9.6$ Hz, H-1b), 2.31–2.19 (2H, m, H-4), 1.70–1.62 (1H, m, H-3a), 1.55–1.49 (1H, m, H-3b), 1.29 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 1.20 (3H, s, Me-2), 0.90 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.11 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 166.7, 150.0, 120.7, 75.8, 69.7, 60.0, 37.3, 26.6, 25.8, 25.1, 18.2, 14.2, 2.4, – 5.6; HRMS (ES⁺): calc. for $\text{C}_{19}\text{H}_{40}\text{O}_4\text{Si}_2$ $[\text{M}+\text{H}]^+$ 411.2357, found 411.2352

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-5-en-2-ol (86)

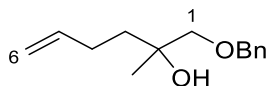


To a solution of CuI (140 mg, 0.74 mmol, 0.1 equiv.) in THF (80 mL) at 0 °C was added allyl magnesium chloride (1.7 M in THF, 17.5 mL, 29.7 mmol, 4.0 equiv.) dropwise. A solution of epoxide **66** (1.49 g, 7.40 mmol, 1.0 equiv.) in Et_2O (1 mL) was then added and the reaction mixture stirred for 2 h. The reaction mixture was quenched with NH_4Cl (50 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 15 mL). Combined organic layers were dried over MgSO_4 and the solvent removed *in vacuo*.

The crude material was purified by flash column chromatography (10:1 PE₃₀₋₄₀/Et₂O) to give the title compound as a colourless oil (1.47 g, 81%)

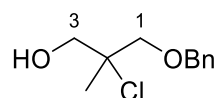
R_f 0.25 (8:1 PE/EtOAc); $[\alpha]_D^{20} + 19.4$ (c 1.00, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 3747, 2960, 2331, 1275, 1115, 935, 836, 770; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 5.92-5.82 (1H, m, H-5), 5.03 (1H, ddt, $J = 17.1, 1.9, 1.7$ Hz, H-6a), 4.94 (1H, ddt, $J = 10.3, 1.9, 1.4$ Hz, H-6b), 3.44 (1H, d, $J = 9.5$ Hz, H-1a), 3.38 (1H, d, $J = 9.5$ Hz, H-1b), 2.33 (1H, s, O-H), 2.19-2.05 (2H, m, H-4), 1.63-1.47 (2H, m, H-3), 1.13 (3H, s, Me-2), 0.91 (9H, s, Si(CH₃)₃), 0.07 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 139.0, 114.1, 72.0, 70.0, 37.6, 28.1, 25.8, 23.0, 18.2, -5.6; **HRMS** (ES⁺): calc. for C₁₃H₂₈O₂Si [M+H]⁺ 267.1751, found 267.1751.

1-(Benzyloxy)-2-methylhex-5-en-2-ol (91)

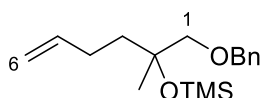


To a suspension of magnesium (240 mg, 10.0 mmol, 2.0 equiv.) and iodine (2 crystals) in Et₂O (2 mL) was added allyl chloride (0.41 mL, 5.00 mmol, 1.0 equiv.) in Et₂O (13 mL) and gently heated to initiate Grignard formation. The reaction mixture was refluxed at 45 °C for 2 h to produce a solution of allyl magnesium chloride (0.25 M). To a solution of epoxide **80** (50.0 mg, 0.28 mmol, 1.0 equiv.) in THF (3 mL) at 0 °C was added CuI (5.7 mg, 0.03 mmol, 0.1 equiv.) and the preformed allyl magnesium chloride (0.25 M, 4.50 mL, 1.12 mmol, 4.0 equiv.). The reaction mixture was stirred for 3 h before being quenched with NH₄Cl (5 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 5 mL). Combined organic layers were dried with MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8:1 PE/EtOAc) to give a 5:1 inseparable mixture of the title alcohol and chloride **83** as a colourless oil (55.0 mg, 4.50 mmol, 90 %).

R_f 0.33 (4:1 PE/EtOAc); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 3260, 2856, 1976, 1640, 1454, 1369, 1102, 910, 737, 698; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.38-7.31 (5H, m, H-Ar), 5.88-5.80 (1H, m, H-5), 5.03 (1H, dq, $J = 17.2, 1.8$ Hz, H-6a), 4.95 (1H, ddt, $J = 10.3, 2.0, 1.2$ Hz, H-6b), 4.58 (2H, s, OCH₂Ar), 3.36 (1H, d, $J = 9.0$ Hz, H-1a), 3.31 (1H, d, $J = 9.0$ Hz, H-1b), 2.24 (1H, s, O-H), 2.18-2.06 (2H, m, H-4), 1.69-1.57 (2H, m, H-3), 1.19 (3H, s, Me-2); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 138.8, 138.0, 128.4, 128.3, 127.6, 114.2, 77.0, 73.3, 71.9, 38.0, 28.0, 23.6.

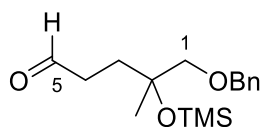
3-(Benzyloxy)-2-chloro-2-methylpropan-1-ol (83)

R_f 0.23 (4:1 PE/EtOAc); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3447, 2860, 1454, 1371, 1093, 1027, 911, 793, 735, 698, 611; **¹H NMR** (400 MHz, CDCl₃): δ_{H} 7.39-7.31 (5H, m, H-Ar), 4.59 (2H, s, CH₂Ar), 3.61 (1H, d, J = 10.7 Hz, H-3a), 3.55 (1H, d, J = 10.7 Hz, H-3b), 3.54 (1H, d, J = 9.2 Hz, H-1a), 3.39 (1H, d, J = 9.2 Hz, H-1b), 2.54 (1H, br s, O-H), 1.29 (3H, s, Me-2); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 137.7, 128.4, 127.8, 127.6, 73.7, 73.4, 72.0, 50.0, 21.9; **HRMS** (ES⁺): calc. for C₁₁H₁₉³⁵ClO₂N [M+NH₄]⁺ 232.1099, found 232.1100.

((1-(Benzyloxy)-2-methylhex-5-en-2-yl)oxy)trimethylsilane (91b)

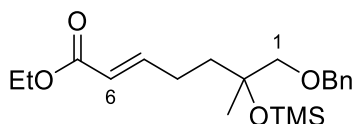
To a solution of alcohol **91** (314 mg, as mixture with **83**, 1.43 mmol, 1.0 equiv.) in CH₂Cl₂ (14 mL) at 0 °C was added imidazole (167 mg, 2.57 mmol, 1.8 equiv.) and chlorotrimethylsilane (0.27 mL, 2.14 mmol, 1.5 equiv.). The reaction mixture was stirred at rt for 2 h before being quenched with NH₄Cl (10 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 5 mL). Combined organic layers were dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10:1 PE/EtOAc) to give the title compound as a colourless oil (355 mg, 1.22 mmol, 85%)

R_f 0.34 (9:1 PE/EtOAc); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2956, 1453, 1249, 1100, 1039, 838, 751, 697, 611; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.32-7.28 (5H, m, H-Ar), 5.88-5.80 (1H, m, H-5), 5.01 (1H, dq, J = 17.2, 1.8 Hz, H-6a), 4.95-4.92 (1H, m, H-6b), 4.55 (2H, s, CH₂Ar), 3.33 (1H, d, J = 9.0 Hz, H-1a), 3.27 (1H, d, J = 9.0 Hz, H-1b), 2.13-2.03 (2H, m, H-4), 1.69-1.63 (1H, m, H-3a), 1.59-1.52 (1H, m, H-3b), 1.26 (3H, s, Me-2), 0.11 (9H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 139.3, 138.5, 128.2, 127.6, 127.5, 113.8, 77.3, 75.3, 73.3, 38.9, 27.9, 24.0, 2.4.

5-(Benzyloxy)-4-methyl-4-((trimethylsilyl)oxy)pentanal (91c)

To a solution of alkene **91b** (386 mg, 1.32 mmol, 1.0 equiv.) in CH₂Cl₂ (30 mL) at –78 °C was bubbled ozone until the solution turned blue. The ozone stream was then replaced with oxygen until the solution returned to colourless. The reaction mixture was quenched with PPh₃ (380 mg, 1.45 mmol, 1.1 equiv.) and slowly warmed to rt. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (15:1 PE/ EtOAc) to give the title compound as a colourless oil (70 % over 3 steps from **80**).

R_f 0.23 (10:1 PE/EtOAc); **IR** (thin film, ν_{max} /cm⁻¹): 3052, 1721, 1584, 1477, 1433, 1249, 1089, 1026, 839, 740, 692, 541, 499; **¹H NMR** (400 MHz, CDCl₃): δ_{H} 9.73 (1H, t, J = 2.0 Hz, H-5), 7.37 – 7.28 (5H, m, H-Ar), 4.53 (1H, d, J = 12.1 Hz, CH_aH_bAr), 4.50 (1H, d, J = 12.1 Hz, CH_aH_bAr), 3.32 (1H, d, J = 9.0 Hz, H-1a), 3.26 (1H, d, J = 9.0 Hz, H-1b), 2.44 (2H, td, J = 7.5, 2.0 Hz, H-4), 1.99-1.95 (1H, m, H-3a), 1.80 (1H, m, H-3b), 1.27 (3H, s, Me-2), 0.09 (9H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 203.1, 149.8, 138.3, 128.4, 127.6, 77.0, 74.9, 73.3, 38.8, 32.6, 25.5, 2.4.

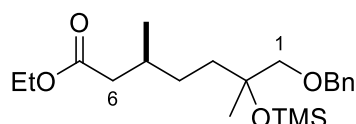
Ethyl (E)-7-(benzyloxy)-6-methyl-6-((trimethylsilyl)oxy)hept-2-enoate (92)

To a slurry of Ba(OH)₂ (280 mg, 1.64 mmol, 1.8 equiv.) in THF (5 mL) at rt was added triethylphosphonoacetate (307 mg, 1.37 mmol, 1.5 equiv.) and the mixture stirred at rt for 45 min. A solution of aldehyde **91c** (268 mg, 0.91 mmol, 1.0 equiv.) in THF: H₂O (40:1, 5 mL) was then added and the reaction mixture stirred at rt for 16 h before being quenched with NH₄Cl (8 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL) and combined organic layers dried with MgSO₄ before the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (10:1 PE/EtOAc) to give the title compound as a colourless oil (291 mg, 0.79 mmol, 87%).

R_f 0.51 (4:1 PE/EtOAc); **IR** (thin film, ν_{max} /cm⁻¹): 2954, 1719, 1654, 1455, 1368, 1250, 1132, 1098, 1041, 830, 751, 698; **¹H NMR** (400 MHz, CDCl₃): δ_{H} 7.34-7.28 (5H, m, H-Ar), 7.01 (1H, dt, J = 15.7, 6.8 Hz, H-5), 5.82 (1H, d, J = 15.7 Hz, H-6), 4.54 (1H, d, J = 12.2 Hz, CH_aH_bAr), 4.51 (1H, d, J = 12.2 Hz, CH_aH_bAr), 4.19 (2H, q, J = 7.20, OCH₂CH₃), 3.32 (1H, d, J = 9.1 Hz, H-1a), 3.25 (1H, d, J = 9.1 Hz, H-1b), 2.30-2.17

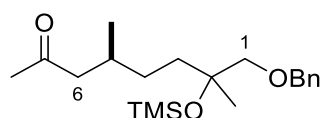
(2H, m, H-4), 1.77-1.71 (1H, m, H-3a), 1.62-1.56 (1H, m, H-3b), 1.29 (3H, t, $J = 7.20$ Hz, OCH_2CH_3), 1.26 (3H, s, Me-2), 0.10 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 166.6, 149.8, 138.3, 129.2, 127.5, 127.4, 120.8, 77.0, 75.1, 73.2, 60.0, 37.9, 26.6, 25.5, 14.2, 2.4; HRMS (ES⁺): calc. for $\text{C}_{20}\text{H}_{32}\text{O}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 387.1962, found 387.1965.

Ethyl (3S)-7-(benzyloxy)-3,6-dimethyl-6-((trimethylsilyl)oxy)heptanoate (93)

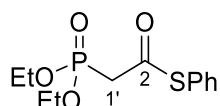


A solution of (*S*)-Tol-BINAP (2.8 mg, 0.0041 mmol, 0.03 equiv.) and CuI (0.5 mg, 0.0027 mmol, 0.02 equiv.) in TBME (0.5 mL) was stirred at rt for 10 min until a yellow suspension formed. The reaction was cooled to -20 °C and MeMgBr (3 M in Et_2O , 0.23 mL, 0.69 mmol, 5.0 equiv.) was added dropwise. After stirring for 15 min, a solution of unsaturated ester **92** (50.0 mg, 0.14 mmol, 1.0 equiv.) in TBME (0.3 mL) was added dropwise over 1 h *via* syringe pump. The reaction mixture was then stirred for a further 1.5 h at -20 °C before being quenched with MeOH (0.25 mL) then NH_4Cl (1 mL). Once warmed to rt, the layers were separated and the aqueous layer extracted with Et_2O (3 x 2 mL). Combined organic layers were dried over MgSO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a colourless oil (16.5 mg, 0.04 mmol, 35%) along with ketone **94** (12.0 mg, 0.03 mmol, 23 %).

R_f 0.34 (6:1 PE/EtOAc); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2962, 1736, 1456, 1371, 1250, 1102, 1036, 830, 751, 698; ^1H NMR (500 MHz, CDCl_3): δ_{H} 7.37-7.28 (5H, m, H-Ar), 4.53 (2H, s, CH_2Ar), 4.13 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 3.29 (1H, d, $J = 9.1$ Hz, H-1a), 3.23 (1H, dd, $J = 9.1, 1.6$ Hz, H-1b), 2.30 (1H, ddd, $J = 14.6, 5.9, 1.5$ Hz, H-6a), 2.12-2.05 (1H, m, H-6b), 1.97-1.85 (1H, m, H-5), 1.56 (3H, s, Me-2), 1.51-1.43 (4H, m, H-3, H-4), 1.26 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 1.22 (3H, d, $J = 2.6$ Hz, Me-5), 0.10 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 169.0, 138.5, 128.2, 127.4, 127.3, 75.5, 73.1, 61.0, 60.0, 37.1, 33.1, 30.4, 28.8, 25.3, 19.7, 14.1, 2.4.

(4R)-8-(Benzyloxy)-4,7-dimethyl-7-((trimethylsilyl)oxy)octan-2-one (94)

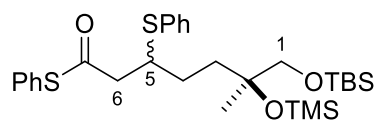
R_f 0.31 (6:1 PE/EtOAc); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2955, 1715, 1454, 1367, 1249, 1099, 1037, 838, 751, 698; **¹H NMR** (400 MHz, CDCl₃): δ_{H} 7.36-7.29 (5H, m, H-Ar), 4.53 (2H, s, H-CH₂Ar), 3.29 (1H, d, $J = 9.1$ Hz, H-1a), 3.23 (1H, dd, $J = 9.1, 1.6$ Hz, H-1b), 2.42 (1H, dd, $J = 16.0, 5.6$ Hz, H-6a), 2.21 (1H, dd, $J = 16.0, 8.3$ Hz, H-6b), 2.12 (3H, s, H-8), 1.99-1.90 (1H, m, H-5), 1.55-1.38 (2H, m, H-4), 1.34-1.13 (2H, m, H-3), 1.22 (3H, d, $J = 2.1$ Hz, Me-2), 0.90 (3H, d, $J = 6.7$ Hz, Me-5), 0.10 (9H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 209.0, 138.5, 128.2, 127.4, 127.3, 75.5, 73.1, 51.1, 37.1, 30.5, 30.2, 29.6, 25.3, 19.8, 2.4; **HRMS** (ES⁺): calc. for C₂₀H₃₄O₃Si [M+H]⁺ 373.2169, found 373.2165.

S-Phenyl 2-(diethoxyphosphoryl)ethanethioate (88)

To a solution of diethylphosphonoacetic acid (0.50 mL, 3.00 mmol, 1.0 equiv.) in CH₂Cl₂ (6 mL) at 0 °C was added thiophenol (0.31 mL, 3.00 mmol, 1.0 equiv.) and DMAP (37.0 mg, 0.30 mmol, 0.1 equiv.). DCC (0.63 g, 3.0 mmol, 1.0 equiv.) was then added portionwise and the reaction mixture stirred for 16 h whilst slowly warming to rt. On completion, the reaction mixture was filtered through Celite®, which was then washed with further CH₂Cl₂ (10 mL). The organic filtrate was washed sequentially with Na₂CO₃ (3 x 5 mL), water (2 x 5 mL) and brine (2 x 5 mL) before being dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3:1 PE/EtOAc → EtOAc) to give the title compound as a colourless oil (697 mg, 2.43 mmol, 81%)

R_f 0.59 (9:1 PE/EtOAc); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1701, 1255, 1018, 994, 956, 748, 690, 582, 537, 474; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.43 (5H, s, H-Ar), 4.20 (4H, app quint., $J = 7.2$ Hz, CH₂CH₃), 3.31 (2H, d, $J_{\text{H-P}} = 21.2$ Hz, H-1'), 1.37 (6H, t, $J = 7.2$ Hz, CH₂CH₃); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 188.5, 134.3, 129.7, 129.3, 127.2, 62.9, 42.8, 16.3; **HRMS** (ES⁺): calc. for C₁₂H₁₇O₄PS [M+H]⁺ 289.0658, found 289.0658.

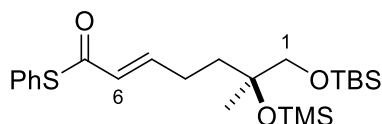
S-Phenyl-(6S)-7-((tert-butyldimethylsilyl)oxy)-6-methyl-3-(phenylthio)-6-((trimethylsilyl)oxy)heptanethioate (90)



To a slurry of Ba(OH)₂ (95.4 mg, 0.56 mmol, 1.8 equiv.) in THF (1.0 mL) at rt was added a solution of phosphonate **88** (135 mg, 0.47 mmol, 1.5 equiv.) in THF (0.5 mL) and the mixture stirred for 45 min. A solution of aldehyde **85** (100 mg, 0.31 mmol, 1.0 equiv.) in THF: H₂O (40:1, 1.5 mL) was added dropwise and the reaction mixture stirred for a further 16 h. The reaction was quenched with NH₄Cl (2 mL) and the organic layer extracted with Et₂O (3 x 5 mL). Combined organic layers were dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (25:1 PE/EtOAc) to give an inseparable diastereomeric mixture of **90** and **89** in a 1:1 ratio (135 mg, 0.29 mmol, 95%).

R_f 0.59 (9:1 PE/EtOAc); **IR** (combined, thin film, ν_{max} /cm⁻¹): 2954, 1692, 1633, 1472, 1250, 1099, 1024, 966, 834, 776, 744, 688; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.50-7.27 (10H, m, H-Ar), 3.65-3.59 (1H, m, H-5), 3.42 (1H, d, *J* = 9.8 Hz, H-1a), 3.35 (1H, d, *J* = 9.6 Hz, H-1b), 2.96 (1H, dd, *J* = 15.4, 6.3 Hz, H-6a), 2.89 (1H, dd, *J* = 15.4, 7.6 Hz, H-6b), 1.82-1.72 (2H, m, H-4), 1.67-1.62 (1H, m, H-3a), 1.59-1.53 (1H, m, H-3b), 1.21 (3H, s, Me-2), 0.93 (9H, s, Si(CH₃)₃), 0.12 (9H, s, Si(CH₃)₃), 0.08 (6H, s, Si(CH₃)₂); **¹³C NMR** (combined, 125 MHz, CDCl₃): δ_{C} 195.4, 188.1, 147.8, 134.7, 134.0, 123.7, 129.4, 129.3, 129.2, 129.1, 129.0, 127.8, 127.6, 127.4, 127.3, 76.1, 75.9, 70.1, 70.0, 69.9, 49.1, 45.7, 37.4, 36.5, 28.5, 26.9, 26.0, 25.2, 25.0, 18.3, 2.62, – 5.3, – 5.4; **HRMS** (ES⁺): calc. for C₂₉H₄₆O₃Si₂S₂ [M+H]⁺ 563.2500, found 563.2489.

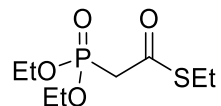
S-Phenyl-(S,E)-7-((tert-butyldimethylsilyl)oxy)-6-methyl-6-((trimethylsilyl)oxy)hept-2-enethioate (89)



R_f 0.37 (10:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.43 (5H, s, H-Ar), 7.07 (1H, dt, *J* = 15.5, 6.8 Hz, H-5), 6.22 (1H, dt, *J* = 15.5, 1.5 Hz, H-6), 3.46 (1H, d, *J* = 9.6 Hz, H-1a), 3.38 (1H, d, *J* = 9.6 Hz, H-1b), 2.39-2.27 (2H, m, H-4), 1.72-1.70 (1H, m, H-3a), 1.62-1.59 (1H, m, H-3b), 1.25 (3H, s, Me-2), 0.94 (9H,

s, SiC(CH₃)₃), 0.16 (9H, s, Si(CH₃)₃), 0.09 (6H, s, Si(CH₃)₂); **HRMS** (ES+): calc. for C₂₃H₄₀O₃Si₂S [M+H]⁺ 453.2309, found 453.2301.

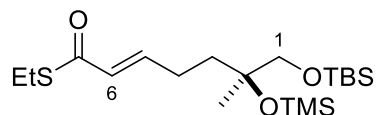
S-Ethyl 2-(diethoxyphosphoryl)ethanethioate (**91**)



To a solution of diethylphosphonoacetic acid (0.5 mL, 3.00 mmol, 1.0 equiv.) in CH₂Cl₂ (6 mL) at 0 °C was added ethanethiol (0.22 mL, 3.00 mmol, 1.0 equiv.) and DMAP (37.0 mg, 0.30 mmol, 0.1 equiv.) and stirred for 5 min. DCC (0.63 g, 3.00 mmol, 1.0 equiv.) was then added in 5 portions. The reaction mixture was slowly warmed to rt and stirred for 16 h before being filtered through Celite®, which was then washed with CH₂Cl₂ (10 mL). The filtrate was then washed with NaHCO₃ (2 x 8 mL), H₂O (8 mL) and brine (8 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (2:1 PE/Et₂O → Et₂O). Remaining 1,3 dicyclohexyl urea was filtered off to give the title compound as a colourless oil (563 mg, 78%)

R_f 0.17 (2:1 PE/EtOAc); **IR** (thin film, ν_{max} /cm⁻¹): 2982, 2933, 1681, 1452, 1393, 1256, 1164, 1008, 966, 823, 703, 668; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 4.18 (2H, qd, J = 6.9, 1.8 Hz, 2 x OCHaHbCH₃), 4.16 (2H, qd, J = 6.9, 1.3 Hz, 2 x OCHaHbCH₃), 3.21 (2H, d, J = 21.3 Hz, H-1), 2.92 (2H, q, J = 7.4 Hz, SCH₂CH₃), 1.34 (6H, t, J = 6.9 Hz, OCH₂CH₃)₂, 1.27 (3H, t, J = 7.4 Hz, SCH₂CH₃); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 190.1, 62.6, 43.2, 42.1, 24.0, 16.2, 16.1, 14.3; **HRMS** (ES+): calc. for C₈H₁₈O₄PS [M+H]⁺ calc. 241.0658, found 241.0656.

S-Ethyl(*S,E*)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-6-((trimethylsilyl)oxy)hept-2-enethioate (**69**)

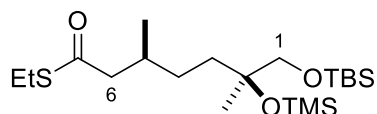


To a suspension of dry LiCl (11.9 mg, 0.28 mmol, 1.8 equiv.) in THF (0.75 mL) at – 35 °C was added a solution of phosphonate **91** (68.0 mg, 0.28 mmol, 1.8 equiv.) in THF (0.3 mL) and the reaction mixture stirred for 10 min. Et₃N (39 μ L, 0.28 mmol, 1.8 equiv.) was then added and the reaction mixture stirred for a further 10 min. A solution of aldehyde **85** (50.0 mg, 0.16 mmol, 1.0 equiv.) in THF (0.75 mL) was subsequently added and the resulting suspension stirred for 16 h, maintaining a temperature of –35 °C. The reaction was then quenched with NH₄Cl (3 mL), the layers separated and the aqueous layer

extracted with Et₂O (3 x 3 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40:1 PE/EtOAc) to give the title compound as a colourless oil (52.3 mg, 80%, 94% brsm).

R_f 0.38 (20:1 PE/EtOAc); $[\alpha]_D^{20} + 16.5$ (c 0.45, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 2955, 2930, 2858, 1677, 1634, 1463, 1251, 1102, 1024, 830, 776, 668; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 6.95 (1H, dt, $J = 15.5, 6.8$ Hz, H-5), 6.12 (1H, dt, $J = 15.5, 1.5$ Hz, H-6), 3.42 (1H, d, $J = 9.6$ Hz, H-1a), 3.35 (1H, d, $J = 9.6$ Hz, H-1b), 2.96 (2H, q, $J = 7.5$ Hz, SCH₂CH₃), 2.33-2.20 (2H, m, H-4), 1.68 (1H, ddd, $J = 13.5, 10.3, 6.1$ Hz, H-3a), 1.55 (1H, ddd, $J = 13.5, 10.3, 5.6$ Hz, H-3b), 1.30 (3H, t, $J = 7.5$ Hz, SCH₂CH₃), 1.22 (3H, s, Me-2), 0.92 (9H, s, Si(CH₃)₃), 0.13 (9H, s, Si(CH₃)₃), 0.07 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 190.1, 146.1, 128.2, 75.8, 69.8, 37.3, 26.6, 25.8, 25.1, 22.9, 18.2, 14.7, 2.5, -5.5; **HRMS** (ES⁺): calc. for C₁₉H₄₁O₃SSi₂ [M+H]⁺ calc. 405.2309, found 405.2310.

S-Ethyl (3S,6S)-7-((tert-butyldimethylsilyl)oxy)-3,6-dimethyl-6-((trimethylsilyl)oxy) heptanethioate (71)

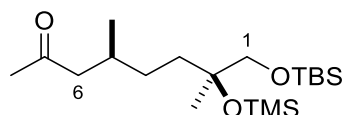


CuI (0.9 mg, 4.75 μmol , 0.05 equiv) and (S)-Tol-BINAP (3.5 mg, 5.23 μmol , 0.055 equiv.) were stirred in Et₂O (1.0 mL) at rt under a yellow suspension was observed, at which point the reaction mixture was cooled to -78 °C. A solution of methyl magnesium bromide (3 M in Et₂O, 0.13 mL, 0.38 mmol, 7.0 equiv.) was added dropwise and the reaction mixture stirred for 10 min. A solution of thioester **69** (23 mg, 0.06 mmol, 1.0 equiv.) in CH₂Cl₂ (0.3 mL) was then added over 5 min and the reaction mixture stirred for 16 h. The reaction was then quenched with MeOH (1 mL) and NH₄Cl (2 mL) and warmed to rt. The layers were then separated and the aqueous layer extracted with Et₂O (3 x 3 mL). Combined organic layers were then dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40:1 PE/EtOAc) to give the title compound as a colourless oil (9.5 mg, 40%, 1.5:1 d.r.) and methyl ketone **100** (11.7 mg, 54%).

R_f 0.63 (2:1 PE/EtOAc); $[\alpha]_D^{20} + 12.3$ (c 0.82, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 2959, 1691, 1394, 1250, 1077, 828, 776, 668; **¹H NMR** (major diastereomer) (500 MHz, CDCl₃): δ_{H} 3.38 (1H, d, $J = 9.6$ Hz, H-1a), 3.29 (1H, dd, $J = 9.6, 6.1$ Hz, H-1b), 2.87 (2H, q, $J = 7.5$ Hz, SCH₂CH₃), 2.54 (1H, ddd, $J = 14.7, 5.9, 3.2$ Hz, H-3a), 2.34 (1H, dt, $J = 14.7, 8.0$ Hz, H-3a), 2.00-1.93 (1H, m, H-5), 1.56-1.28 (4H, m, H-3, H-4), 1.24 (3H,

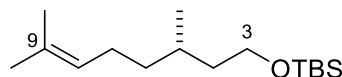
t, $J = 7.5$ Hz, SCH₂CH₃), 1.16 (3H, s, Me-2), 0.93 (3H, d, $J = 6.7$ Hz, Me-5), 0.89 (9H, s, Si(CH₃)₃), 0.09 (9H, s, Si(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ_c 199.2, 76.3, 69.8, 51.6, 36.4, 31.6, 30.3, 25.3, 23.3, 19.6, 18.3, 15.3, 14.8, 2.6, -5.4, -5.5; HRMS (ES⁺): calc. for C₂₀H₄₈NO₃Si₂ [M+NH₄]⁺ calc. 438.2888, found 438.2883.

(4*S*,7*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-4,7-dimethyl-7-((trimethylsilyl)oxy)octan-2-one (100)



¹H NMR (major diastereomer) (500 MHz, CDCl₃): δ_H 3.38 (1H, d, $J = 9.5$ Hz, H-1a), 3.29 (1H, dd, $J = 9.5$, 3.6 Hz, H-1b), 2.42 (1H, dd, $J = 16.0$, 5.5 Hz, H-6a), 2.21 (1H, ddd, $J = 16.0$, 7.2, 2.0 Hz, H-6b), 2.12 (3H, s, COCH₃), 1.97-1.90 (1H, m, H-5), 1.33-1.22 (4H, m, H-4, H-3), 1.16 (3H, s, Me-2), 0.89 (9H, s, Si(CH₃)₃), 0.87 (3H, d, $J = 6.5$ Hz, Me-5), 0.09 (9H, s, Si(CH₃)₃), 0.03 (6H, s, Si(CH₃)₂);

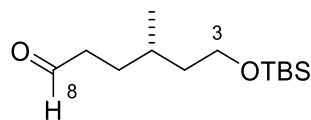
(*S*)-*tert*-Butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (106)



To a solution of β -citronellol (1.16 mL, 6.40 mmol, 1.0 equiv.) in CH₂Cl₂ (40 mL) were added imidazole (653 mg, 9.60 mmol, 1.5 equiv.) and DMAP (39.0 mg, 0.32 mmol, 0.05 equiv.). TBSCl (1.25 g, 8.32 mmol, 1.2 equiv.) was then added in 5 portions and the reaction mixture stirred at rt for 90 min before being quenched with NH₄Cl (30 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 25 mL). Combined organic layers were dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20:1 PE/EtOAc) to give the title compound as a colourless oil (1.56 g, 90 %).

¹H NMR (500 MHz, CDCl₃): δ_H 5.09 (1H, t, $J = 7.2$ Hz, H-8), 3.67-3.58 (2H, m, H-3), 2.03-1.90 (2H, m, H-7), 1.67 (3H, s, Me-9a), 1.59 (3H, s, Me-9b), 1.58-1.51 (2H, m, H-4), 1.35-1.29 (2H, m, H-6), 1.17-1.10 (1H, m, H-5), 0.88 (9H, s, Si(CH₃)₃), 0.87 (3H, d, $J = 6.6$ Hz, Me-5); HRMS (ES⁺): calc. for C₁₆H₃₅OSi [M+H]⁺ calc. 271.2452, found 271.2449.

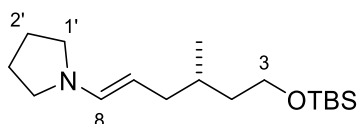
Data in agreement with literature values¹⁶⁶

(S)-6-((tert-Butyldimethylsilyl)oxy)-4-methylhexanal (107)

Alkene **106** (615 mg, 2.27 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (23 mL) and cooled to -78°C . Ozone was then bubbled through until a persistent blue colour was observed. At this point the gas inlet was replaced with oxygen until the blue colour dissipated. PPh_3 (894 mg, 3.41 mmol, 1.5 equiv.) was then added and the reaction mixture stirred for 1 h. After the addition of PE (30 mL), the precipitate was filtered through Celite® and the filtrate concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE \rightarrow 20:1 PE/EtOAc) to give the title compound as a colourless oil (405 mg, 74%).

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1727, 1472, 1388, 1255, 1094, 834, 775; **^1H NMR** (500 MHz, CDCl_3): δ_{H} 9.77 (1H, t, $J = 1.8$ Hz, H-8), 3.69-3.60 (2H, m, H-3), 2.50-2.38 (2H, m, H-7), 1.71-1.43 (5H, m, H-4, H-5, H-6), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.86 (3H, d, $J = 6.6$ Hz, Me-5), 0.04 (6H, s, $\text{Si}(\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3): δ_{C} 202.7, 60.9, 41.6, 39.4, 29.1, 28.8, 25.8, 19.2, 18.2, -5.4 , -5.4 ; **HRMS** (ES $^+$): calc. for $\text{C}_{13}\text{H}_{29}\text{OSi}$ $[\text{M}+\text{H}]^+$ calc. 245.1931, found 245.1935.

Data in agreement with literature values.¹⁶⁶

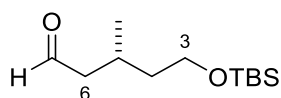
(S,E)-1-(6-((tert-Butyldimethylsilyl)oxy)-4-methylhex-1-en-1-yl)pyrrolidine (113)

To a solution of aldehyde **107** (50.0 mg, 0.21 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL) were added pyrrolidine (34 μL , 0.42 mmol, 2.0 equiv.) and 4Å MS (25 mg, 50 wt%) and stirred for 2 h. With only starting material observed by TLC, K_2CO_3 (43.0 mg, 0.31 mmol, 1.5 equiv.) was added and the reaction mixture stirred for a further h, before being quenched with NaHCO_3 (1 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 1 mL). Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude enamine (52 mg, 85%), which was used in the following reaction without further purification.

R_f 0.32 (15:1 PE/EtOAc); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2928, 1644, 1462, 1254, 1093, 823, 775, 663; **^1H NMR** (500 MHz, CDCl_3): δ_{H} 6.13 (1H, d, $J = 13.6$ Hz, H-8), 4.08 (1H, dt, $J = 13.6$, 7.3 Hz, H-7), 3.66-3.59 (2H, m,

H-3), 3.13-3.00 (4H, m, H-1'), 1.87-1.78 (4H, m, H-2'), 1.65-1.25 (5H, m, H-4, H-5, H-6), 0.89 (9H, s, Si(CH₃)₃), 0.86 (3H, d, *J* = 6.8 Hz, Me-5), 0.04 (6H, s, Si(CH₃)₂).

(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-methylpentanal (111**)**



Procedure A:

To a stirred solution of ester **128** (2.0 g, 7.69 mmol, 1.0 equiv.) in (80 mL) at –78 °C was added DIBAL (1 M in hexanes, 8.08 mL, 8.08 mmol, 1.05 equiv.) dropwise. The reaction mixture was maintained at this temperature for 1 h, before being quenched with NaK tartrate (60 mL) and stirred for a further h whilst warming to rt. The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 40 mL). Combined organic extracts were dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give the title compound as a colourless oil (1.63 g, 92%)

Procedure B:

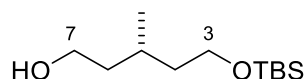
To a stirred solution of aldehyde **107** (250 mg, 1.02 mmol, 1.0 equiv.) in DMF (0.3 mL) were added TMSCl (0.18 mL, 1.43 mmol, 1.4 equiv.) and Et₃N (0.37 mL, 2.66 mmol, 2.6 equiv.) The reaction mixture was then heated to 140 °C for 2 h. After cooling to rt, the reaction was quenched with NaHCO₃ (0.5 mL) and extracted with PE (3 x 1 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*.

The crude residue was then redissolved in CH₂Cl₂ (3 mL), cooled to –78 °C and a stream of ozone bubbled through. Once the solution had turned blue, the stream was replaced with oxygen until the solution became colourless. PPh₃ (393 mg, 1.53 mmol, 1.5 equiv.) was then added and the reaction mixture warmed to rt before stirring for a further h. PE (5 mL) was then added to precipitate out the triphenylphosphine oxide, which was removed by filtration. The filtrate was concentrated *in vacuo* and the crude residue purified by flash column chromatography (PE → 20:1 PE/EtOAc) to give the title compound as a colourless oil (67 mg, 30% over both steps).

R_f 0.37 (9:1 PE/EtOAc); **IR** (thin film, ν_{max} /cm⁻¹): 1727, 1256, 1095, 913, 836, 774, 743; **¹H NMR** (400 MHz, CDCl₃): δ_{H} 9.75 (1H, t, *J* = 2.3 Hz, H-7), 3.67 (1H, t, *J* = 6.4, 2.6 Hz, H-3), 2.46 (1H, ddd, *J* = 10.4, 8.6, 2.3 Hz, H-6a), 2.26 (1H, ddd, *J* = 10.4, 7.8, 2.3 Hz, H-6b), 1.61-1.43 (3H, m, H-5, H-4), 0.99 (3H, d, *J* = 6.5

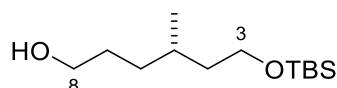
Hz, Me-5), 0.90 (9H, s, Si(CH₃)₃), 0.05 (6H, s, Si(CH₃)₂) ; ¹³C NMR (125 MHz, CDCl₃): δ_C 202.8, 60.7, 50.9, 39.5, 25.9, 25.1, 20.0, 18.3, –5.4; HRMS (ES⁺): calc. for C₁₂H₂₇O₂Si [M+H]⁺ 231.1775, found 231.1776. Data in accordance with literature values.¹⁶⁷

(S)-5-((tert-Butyldimethylsilyl)oxy)-3-methylpentan-1-ol



R_f 0.24 (9:1 PE/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ_H 3.75-3.62 (4H, m, H-7, H-3), 1.78-1.37 (5H, m, H-6, H-5, H-4), 0.93 (3H, d, *J* = 6.7 Hz, Me-5), 0.90 (9H, s, Si(CH₃)₃), 0.06 (6H, s, Si(CH₃)₂). Data in agreement with literature values.¹⁶⁸

(S)-6-((tert-Butyldimethylsilyl)oxy)-4-methylhexan-1-ol (116)



Procedure A:

To a solution of aldehyde **107** (300 mg, 1.25 mmol, 1.0 equiv.) in MeOH (10 mL) at 0 °C was added NaBH₄ (35.0 mg, 0.94 mmol, 0.75 equiv.) and stirred for 20 min. The reaction was then quenched with NH₄Cl (8 mL) and Et₂O (5 mL), the layers extracted and the aqueous layer extracted with Et₂O (3 x 5 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless liquid (180 mg, 60%).

Procedure B:

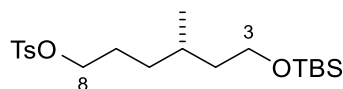
Alkene **106** (1.70 g, 6.30 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (40 mL) and cooled to –78 °C. A stream of ozone was bubbled through the solution until a blue colour was observed, at which point oxygen was bubbled through until the blue colour dissipated. NaBH₄ (177 mg, 4.73 mmol, 0.75 equiv.) was then added, the reaction mixture warmed to rt and stirred for 1 h. The solvent was then removed *in vacuo* and the residue purified by flash column chromatography (10:1 → 6:1 PE/EtOAc) to give the title compound as a colourless liquid (1.29 g, 79%).

R_f 0.18 (10:1 PE/EtOAc); IR (thin film, ν_{max}/cm⁻¹): 3363, 1472, 1255, 1096, 823, 775; ¹H NMR (500 MHz, CDCl₃): δ_H 3.71-3.60 (4H, m, H-8, H-3), 1.65-1.17 (7H, m, H-7, H-6, H-5, H-4), 0.90 (3H, d, *J* = 6.8 Hz, Me-

5), 0.89 (9H, s, Si(CH₃)₃), 0.05 (6H, s, Si(CH₃)₂); **HRMS** (ES⁺): calc. for C₁₃H₃₁O₂Si [M+H]⁺ 247.2088, found 247.2089.

Data in agreement with literature values¹⁶⁹

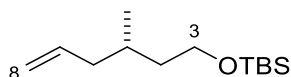
(S)-6-((*tert*-Butyldimethylsilyl)oxy)-4-methylhexyl 4-methylbenzenesulfonate (123)



To a solution of alcohol **116** (180 mg, 0.83 mmol, 1.0 equiv.) in CH₂Cl₂ (8 mL) at rt was added tosyl chloride (471 mg, 2.48 mmol, 3.0 equiv.) and Et₃N (0.58 mL, 4.15 mmol, 5.0 equiv.) and stirred for 3 h. The reaction was then quenched with NaHCO₃ (8 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), combined organic layers dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (10:1 PE/EtOAc) to give the title compound as a colourless oil (275 mg, 94%).

R_f 0.44 (9:1 PE/EtOAc); [α]_D²⁰ + 6.7 (c 0.85, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 3104, 1520, 1474, 1083, 984, 839, 770; **¹H NMR** (500 MHz, CDCl₃): δ _H 7.79 (2H, d, *J* = 8.3 Hz, H-Ar), 7.34 (2H, d, *J* = 8.3 Hz, H-Ar), 4.02 (2H, t, *J* = 6.4 Hz, H-8), 3.64-3.56 (2H, m, H-3), 2.45 (3H, s, Ar-Me), 1.71-1.46 (6H, m, H-7, H-6, H-4), 1.33-1.30 (1H, m, H-5), 0.88 (9H, s, Si(CH₃)₃), 0.87 (3H, d, *J* = 6.8 Hz, Me-5), 0.03 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ _C 144.7, 133.2, 129.8, 127.9, 70.8, 62.7, 39.3, 35.2, 26.3, 25.7, 21.6, 19.3, 19.2, 18.1, – 2.9; **HRMS** (ES⁺): calc. for C₂₀H₃₇O₄SSi [M+H]⁺ 401.2176, found 401.2179.

(S)-*tert*-Butyldimethyl((3-methylhex-5-en-1-yl)oxy)silane (119)

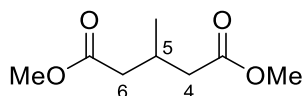


To a solution of alcohol **116** (30.0 mg, 0.12 mmol, 1.0 equiv.) in THF (1.5 mL) was added 2-nitrophenyl selenocyanate (36.0 mg, 0.16 mmol, 1.3 equiv.) and then tributylphosphine (40 μ L, 0.16 mmol, 1.3 equiv.) before being stirred for 1 h. H₂O₂ (30% aq, 0.2 mL, 1.60 mmol, 13.0 equiv.) was then added and the reaction mixture stirred for 20 h, before being quenched with NaHCO₃ (2 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 2 mL). Combined organic layers were washed with brine (3 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (20:1 PE/EtOAc) to give the title compound as a colourless oil (17 mg, 60%).

R_f 0.35 (20:1 PE/EtOAc); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1599, 1472, 1362, 1180, 1097, 835, 776, 664; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 5.80-5.74 (1H, m, H-7), 5.02-4.96 (2H, m, H-8), 3.69-3.59 (2H, m, H-3), 2.07 (1H, dddd, $J = 13.5, 6.2, 6.2, 1.1$ Hz, H-6a), 1.90 (1H, ddd, $J = 13.5, 7.3, 7.2$ Hz, H-6b), 1.69-1.52 (2H, m, H-4), 1.37-1.29 (1H, m, H-5), 0.88 (9H, s, Si(CH₃)₃), 0.87 (3H, d, $J = 6.1$ Hz, Me-5), 0.03 (6H, s, Si(CH₃)₂).

Data in agreement with literature values¹⁷⁰

Dimethyl 3-methylpentanedioate (**120**)

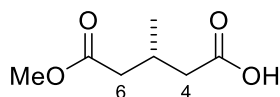


To a stirred solution of 3-methylglutaric acid (19.0 g, 13.0 mmol, 1.0 equiv.) in MeOH (250 mL) at 0 °C was added acetyl chloride (37.1 mL, 52.0 mmol, 4.0 equiv.) dropwise. The reaction mixture was heated to reflux for 3 h. The solvent was removed *in vacuo* and the residue redissolved in NaHCO₃ (100 mL) to neutralise. Once gas evolution had ceased, the product was extracted with CH₂Cl₂ (4 x 80 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give the product as a yellow oil (20.2 g, 89%), which was used without further purification.

R_f 0.61 (2:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_{H} 3.68 (6H, s, CO₂Me), 2.52-2.42 (1H, m, H-5), 2.40 (2H, dd, $J = 15.0, 6.0$ Hz, H-4a, H-6a), 2.25 (2H, dd, $J = 15.0, 7.3$ Hz, H-4b, H-6b), 1.03 (3H, d, $J = 6.5$ Hz, Me-5); **HRMS** (ES⁺): calc. for C₈H₁₅O₄ [M+H]⁺ 175.0965, found 175.0962.

Data in agreement with literature values.¹⁷¹

(*R*)-5-Methoxy-3-methyl-5-oxopentanoic acid (**121**)



A solution of diester **120** (10.0 g, 57.1 mmol, 1.0 equiv.) in MeOH (44.5 mL) and pH 7 buffer (KH₂PO₄/Na₂HPO₄, 0.1 M, 220 mL) was cooled to –10 °C and pig liver esterase (550 mg, 9900 U) added. A solution of NaOH (1.0 M *aq*, 57.1 mL, 57.1 mmol, 1.0 equiv.) was added dropwise over 54 h, at such a rate as to maintain a pH between 6.5 and 8.0. After the addition was completed, the light brown suspension was filtered through Celite® and the residue rinsed with H₂O (150 mL). The pH of the combined filtrates was adjusted to 3 with HCl (3M *aq*) and the mixture extracted with Et₂O (8 x 250

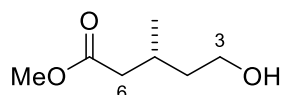
mL). Combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to give the title compound (8.92 g, 55.3 mmol, 97%) as a colourless liquid.

Enantioenriched monoester **121** was dissolved in acetone (180 mL) and cinchonidine (16.8 g 57.1 mmol, 1.0 equiv.) added. The white suspension was heated to 40 °C and stirred rapidly. H₂O (23 mL) was added dropwise until a pale-yellow solution formed. The solution was cooled to rt and then left to stand at – 5 °C for 16 h to give off-white, needle like crystals. The solid was collected by filtration, washed with ice-cold acetone (35 mL) and dried *in vacuo*. The mother liquor was recooled to – 10 °C, left to stand for 16 h, filtered and the solids washed (acetone, 20 mL) and collected, to isolate a second crop of the crystals. Combined collected solids were dissolved in HCl (2M, 120 mL) and extracted with Et₂O (5 x 150 mL). The organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to yield the title compound as a colourless oil (5.53 g, 34.3 mmol, 62%, 96% ee).

R_f 0.24 (1:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_H 3.70 (3H, s, OCH₃), 2.53-2.42 (3H, m, H-4a, H-5, H-6a), 2.35-2.27 (2H, m, H-4b, H-6b), 1.08 (3H, d, *J* = 6.5 Hz, Me-5); **HRMS** (ES⁺): calc. for C₇H₁₀O [M-H]– 159.0663, found 159.0665. **R_T** (R) 165.6 min, **R_T** (S) 172.0 min, total run time 240 min.

Data in agreement with literature values.⁸⁸

Methyl (*R*)-5-hydroxy-3-methylpentanoate (**127**)

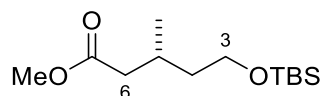


To a stirred solution of carboxylic acid **121** (2.00 g, 12.5 mmol, 10.0 equiv.) in THF (200 mL) at 0 °C was added BH₃·DMS (6.8 mL, 13.75 mL, 1.1 equiv.) dropwise. The reaction mixture stirred for 1 h. NaHCO₃ (150 mL) was then added and the layers separated. The aqueous layer was extracted with Et₂O (3 x 100 mL) and combined organic extracts dried over MgSO₄ before the solvent was carefully removed *in vacuo*. The crude material was used directly in the following reaction without further purification.

R_f 0.45 (1:1 PE/EtOAc); **¹H NMR** (400 MHz, CDCl₃): δ_H 3.70-3.67 (2H, m, H-3), 3.68 (3H, s, OMe), 2.34 (1H, dd, *J* = 14.7, 6.5 Hz, H-6a), 2.21 (1H, dd, *J* = 14.7, 7.1 Hz, H-6b), 2.20-2.10 (1H, m, H-5), 1.65 (1H, br s, O-H), 1.61-1.49 (2H, m, H-4), 0.99 (3H, d, *J* = 6.7 Hz, Me-5); **IR** (thin film, ν_{max}/cm^{–1}): 3452, 2958, 1733, 1437, 1292, 1212, 1165, 1059, 1014, 846; **HRMS** (ES⁺): calc. for C₇H₁₅O₃ [M+H]⁺ 147.1016, found 147.1012.

Data in agreement with literature values¹⁷²

Methyl (*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-methylpentanoate (128**)**

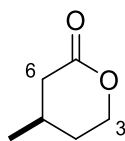


To a stirred solution of crude alcohol **127** (1.82 g, 12.5 mmol, 1.0 equiv.) in CH₂Cl₂ (125 mL) was added imidazole (1.02 g, 15 mmol, 1.2 equiv.), then TBSCl (2.07 g, 13.75 mmol, 1.2 equiv.) The reaction mixture was stirred for 90 min before being quenched with NH₄Cl (80 mL). The layers were separated and the aqueous layer extracted with further CH₂Cl₂ (3 x 50 mL). Combined organic extracts were dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (2.98 g, 92% over two steps).

¹H NMR (500 MHz, CDCl₃): δ_H 3.69-3.61 (2H, m, H-3), 3.66 (3H, s, OMe), 2.36 (1H, dd, *J* = 12.9, 5.0 Hz, H-6), 2.17-2.04 (2H, m, H-6, H-5), 1.60-1.52 (1H, m,) 1.46-1.38 (1H, m), 0.96 (3H, d, *J* = 6.5 Hz, Me-5), 0.89 (9H, s, SiC(CH₃)₃), 0.04 (9H, s, Si(CH₃)₂); **HRMS** (ES⁺): calc. for C₁₄H₃₁O₃Si [M+H]⁺ 275.2037, found 275.2038.

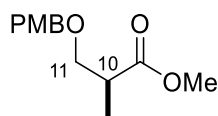
Data in agreement with literature values¹⁷³

(*R*)-4-Methyltetrahydro-2H-pyran-2-one (125**)**



¹H NMR (400 MHz, CDCl₃): δ_H 4.43 (1H, dt, *J* = 11.3, 4.4 Hz, H-3a), 4.27 (1H, ddd, *J* = 11.3, 10.7, 3.8 Hz, H-3b), 2.68 (1H, dd, *J* = 11.7, 1.3 Hz, H-6a), 2.28-2.05 (2H, m, H-4), 1.93 (1H, dd, *J* = 11.7, 4.0 Hz, H-6b), 1.58-1.50 (1H, m, H-5), 1.08 (3H, d, *J* = 6.4 Hz, Me-5).

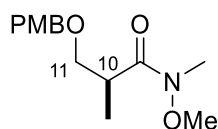
Data in agreement with literature values¹⁷⁴

Methyl (S)-3-((4-methoxybenzyl)oxy)-2-methylpropanoate (133)

To a stirred solution of (S)-Roche ester (15.6 g, 132 mmol, 1.0 equiv.) in CH_2Cl_2 (300 mL) were sequentially added PMBTCA (50.0 g, 198 mmol, 1.5 equiv.) and PPTS (3.31 g, 13.2 mmol, 0.1 equiv.) The reaction mixture was stirred for 16 h before being quenched with NaHCO_3 (200 mL). The layers were separated and the aqueous layer extracted with further CH_2Cl_2 (3 x 100 mL). Combined organic layers were washed with brine (100 mL) and dried over MgSO_4 . The crude material was purified by flash column chromatography (9:1 \rightarrow 6:1 PE/EtOAc) to give the title compound as a colourless oil (25 g, 81%).

R_f 0.38 (4:1 PE/EtOAc); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.23 (2H, d, $J = 8.7$, H-Ar), 6.87 (2H, d, $J = 8.7$ Hz), 4.46 (1H, d, $J = 11.9$ Hz, $\text{OCH}_a\text{H}_b\text{Ar}$), 4.44 (1H, d, $J = 11.9$ Hz, $\text{OCH}_a\text{H}_b\text{Ar}$), 3.80 (3H, s, ArOCH_3), 3.69 (3H, s, CO_2CH_3), 3.63 (1H, dd, $J = 9.2, 7.4$ Hz, H-11a), 3.46 (1H, dd, $J = 9.2, 6.0$ Hz, H-11b), 2.77 (1H, dtd, $J = 7.4, 7.1, 6.0$ Hz, H-10), 1.16 (3H, d, $J = 7.1$ Hz, Me-10).

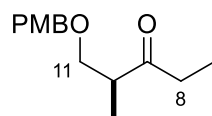
Data in agreement with literature values.¹⁷⁵

(S)-N-Methoxy-3-((4-methoxybenzyl)oxy)-N,2-dimethylpropanamide (129)

To a slurry of *N*, *O*- dimethylhydroxylamine hydrochloride (15.7 g, 158 mmol, 1.5 equiv.) and methyl ester **133** (25.0 g, 105 mmol, 1.0 equiv.) in THF (180 mL) was added *i*-PrMgCl (3 M in Et_2O , 155 mL, 473 mmol, 4.5 equiv.) over 30 min, maintaining a temperature of -20°C . The reaction mixture was then stirred at -10°C for a further 3 h before quenching with NH_4Cl (200 mL). The layers were separated and the aqueous layer extracted with EtOAc (5 x 50 mL). The crude material was purified by flash column chromatography (4:1 \rightarrow 1:1 PE/EtOAc) to give the title compound as an orange liquid (23.8 g, 85%).

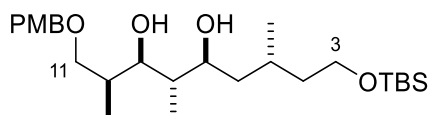
R_f 0.18 (3:1 PE/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.23 (2H, d, $J = 8.6$ Hz, H-Ar), 6.86 (2H, d, $J = 8.6$ Hz, H-Ar), 4.48 (1H, d, $J = 11.7$ Hz, $\text{OCH}_a\text{H}_b\text{Ar}$), 4.40 (1H, d, $J = 11.7$ Hz, $\text{OCH}_a\text{H}_b\text{Ar}$), 3.79 (3H, s, ArOCH_3), 3.69 (1H, app t, $J = 8.8$ Hz, H-11a), 3.68 (3H, s, $\text{N}(\text{CH}_3)\text{OCH}_3$), 3.39 (1H, dd, $J = 8.8, 5.9$ Hz, H-11b), 3.28 - 3.22 (1H, m, H-10), 3.20 (3H, s, $\text{N}(\text{CH}_3)\text{OMe}$), 1.10 (3H, d, $J = 6.8$ Hz, Me-10).

Data in agreement with literature values.¹⁷⁶

(S)-1-((4-Methoxybenzyl)oxy)-2-methylpentan-3-one (45)

To a stirred solution of Weinreb amide **129** (4.5 g, 16.9 mmol, 1.0 equiv.) in THF (80 mL) at 0 °C was added EtMgBr (1M in Et₂O, 42 mL, 42 mmol, 2.5 equiv.). The reaction mixture was stirred for 2 h before quenching with NH₄Cl (70 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 40 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a pale-yellow liquid (3.50 g, 88%).

R_f 0.32 (9:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_H 7.21 (2H, d, *J* = 8.6 Hz, H-Ar), 6.87 (2H, d, *J* = 8.6 Hz, H-Ar), 4.43 (1H, d, *J* = 11.6 Hz, OCH₂aH_bAr), 4.39 (1H, d, *J* = 11.6 Hz, OCH_abH_bAr), 3.80 (3H, s, ArOMe), 3.59 (1H, dd, *J* = 9.2, 7.9 Hz, H-11a), 3.42 (1H, dd, *J* = 9.2, 5.5 Hz, H-11b), 2.86 (1H, dtd, *J* = 7.9, 7.1, 5.5 Hz, H-10), 2.50 (2H, q, *J* = 7.3 Hz, H-8), 1.06 (3H, d, *J* = 7.1 Hz, Me-10), 1.04 (3H, t, *J* = 7.3 Hz, CH₂CH₃). Data in agreement with literature values.⁹⁰

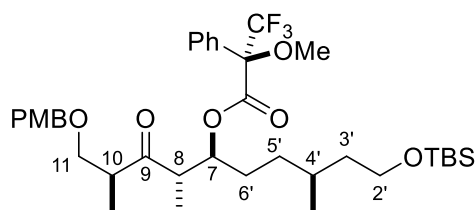
(2S,3R,4S,5S,7R)-9-((tert-Butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-2,4,7-trimethylnonane-3,5-diol (110)

Dicyclohexylboron chloride (6.86 mL, 31.7 mmol, 1.9 equiv.) and Et₃N (4.88 mL, 35.1 mmol, 2.1 equiv.) were sequentially added to Et₂O (60 mL) and cooled to 0 °C before stirring for 10 min. A solution of ketone **45** (7.57 g, 33.5 mmol, 2.0 equiv.) in Et₂O (30 mL) was then added *via* cannula and the reaction mixture stirred for 90 min before cooling to -78 °C. A solution of aldehyde **111** (3.85 g, 16.7 mmol, 1.0 equiv.) in Et₂O (30 mL) was then added *via* cannula and the reaction mixture stirred at this temperature for a further 4 h before being placed in a freezer at -20 °C for 16 h. The reaction mixture was then re-cooled to -78 °C before the dropwise addition of LiBH₄ (4 M in THF, 16.7 mL, 66.8 mmol, 4.0 equiv.). After 2.5 h, the reaction was quenched with NH₄Cl (80 mL) and warmed to rt. The layers

were separated and the aqueous layer extracted with Et₂O (3 x 50 mL). Combined organic extracts were dried over MgSO₄ and the solvent removed *in vacuo*. The crude boronate was purified by flash column chromatography (9:1 → 4:1 PE/EtOAc) to remove excess reduce ketone before being redissolved in MeOH (75 mL). NaOH (10% aq, 45 mL) and H₂O₂ (30% aq, 22.5 mL) were sequentially added and the solution stirred for an h before the product was extracted with Et₂O (3 x 50 mL) and EtOAc (50 mL). Combined organic layers were dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude diol was then repurified by flash column chromatography (9:1 → 4:1 PE/EtOAc) to give the title compound as a colourless oil (6.73 g, 86%).

R_f 0.23 (4:1 PE/EtOAc); $[\alpha]_D^{20} - 16.7$ (c 1.55, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 3425, 1612, 1513, 1463, 1248, 1090, 1038, 980, 835, 775; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.27 (2H, d, $J = 8.7$ Hz, H-Ar), 6.88 (2H, d, $J = 8.7$ Hz, H-Ar), 4.48 (1H, d, $J = 11.6$ Hz, OCH_aH_bAr), 4.45 (1H, d, $J = 11.6$ Hz, OCH_aH_bAr), 3.81 (3H, s, ArOCH₃), 3.78 (1H, dd, $J = 10.3, 1.8$ Hz, H-7), 3.67 (1H, dd, $J = 6.5, 1.4$ Hz, H-11a), 3.66 (1H, dd, $J = 6.5, 1.9$ Hz, H-11b), 3.61-3.58 (2H, m, H-2), 3.34 (1H, dd, $J = 9.0, 6.2$ Hz, H-9), 2.09-1.98 (2H, m, H-8, H-10), 1.52-1.30 (5H, m, H-4, H-5, H-6), 0.90 (3H, d, $J = 6.8$ Hz, Me-10), 0.89 (9H, s, Si(CH₃)₃), 0.80 (3H, d, $J = 6.6$ Hz, Me-8), 0.76 (3H, d, $J = 6.9$ Hz, Me-5), 0.05 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 159.3, 130.0, 129.3, 113.9, 79.1, 75.4, 74.0, 73.2, 61.6, 55.3, 42.1, 41.6, 40.9, 35.1, 26.2, 26.0, 19.4, 18.4, 12.9, 9.4, -5.3; **HRMS** (ES⁺): calc. for C₂₆H₄₇O₅Si [M-H]⁻ 467.3187, found 467.3183.

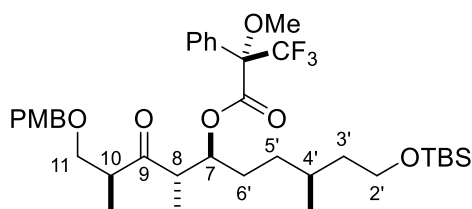
(2S,4S,5S,8S)-10-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-2,4,8-trimethyl-3-oxodecan-5-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (154)



To a solution of alcohol **153** (5.0 mg, 10.4 μmol , 1.0 equiv.) in CH₂Cl₂ (0.5 mL) were added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (12.2 mg, 0.05 mmol, 5.0 equiv.), DCC (10.7 mg, 0.05 mmol, 5.0 equiv.) and DMAP (6.4 mg, 0.05 mmol, 5.0 equiv.). The reaction mixture was stirred for 5 h before being filtered through Celite® and washed with PE (1.0 mL). The filtrate was concentrated in vacuo and the residue passed through a short plug of silica to remove excess (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid.

¹H NMR (500 MHz, CDCl₃): δ_H 7.49-7.35 (5H, m, H-Ar), 7.19 (2H, d, *J* = 8.7 Hz, H-Ar), 6.86 (2H, d, *J* = 8.7 Hz, H-Ar), 5.38 (1H, q, *J* = 5.9 Hz, H-7), 4.40 (1H, d, *J* = 11.6 Hz, OCH_aH_bAr), 4.36 (1H, d, *J* = 11.6 Hz, OCH_aH_bAr), 3.80 (3H, s, ArOCH₃), 3.66-3.55 (3H, m, H-11a, H-2'), 3.52 (3H, s, OCH₃), 3.35 (1H, dd, *J* = 9.1, 5.2 Hz, H-11b), 3.05 (1H, app quint, *J* = 7.1 Hz, H-8), 2.92 (1H, qdd, *J* = 7.0, 5.2, 3.2 Hz, H-10), 1.67-1.62 (2H, m, H-6'), 1.53-1.47 (1H, m, H-4'), 1.28-1.24 (2H, m, H-5'), 1.21 (2H, td, *J* = 7.0, 4.6 Hz, H-3'), 0.98 (3H, d, *J* = 7.2 Hz, H-8), 0.88 (9H, s, Si(CH₃)₃), 0.84 (3H, d, *J* = 6.4 Hz, Me-4'), 0.82 (3H, d, *J* = 7.1 Hz, Me-10), 0.03 (6H, s, Si(CH₃)₂).

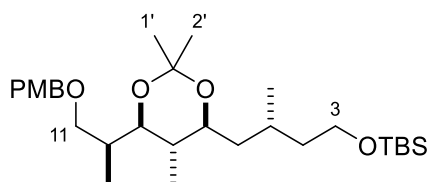
(2S,4S,5S,8S)-10-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-2,4,8-trimethyl-3-oxodecan-5-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (155)



To a solution of alcohol **153** (5.0 mg, 10.4 μmol, 1.0 equiv.) in CH₂Cl₂ (0.5 mL) were added (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (12.2 mg, 0.05 mmol, 5.0 equiv.), DCC (10.7 mg, 0.05 mmol, 5.0 equiv.) and DMAP (6.4 mg, 0.05 mmol, 5.0 equiv.). The reaction mixture was stirred for 5 h before being filtered through Celite® and washed with PE (1.0 mL). The filtrate was concentrated *in vacuo* and the residue passed through a short plug of silica to remove excess MTPA.

¹H NMR (500 MHz, CDCl₃): δ_H 7.57-7.37 (5H, m, H-Ar), 7.19 (2H, d, *J* = 8.6 Hz, H-Ar), 6.85 (2H, d, *J* = 8.6 Hz, H-Ar), 5.37 (1H, td, *J* = 7.1, 3.2 Hz, H-7), 4.41 (1H, d, *J* = 11.6 Hz, CH_aH_bAr), 4.37 (1H, d, *J* = 11.6 Hz, CH_aH_bAr), 3.80 (3H, s, ArOCH₃), 3.61-3.56 (2H, m, H-2'), 3.57 (1H, dd, *J* = 9.1, 3.2 Hz, H-11a), 3.46 (3H, s, OCH₃), 3.39 (1H, dd, *J* = 9.1, 5.2 Hz, H-11b), 3.06 (1H, app quint, *J* = 7.3 Hz, H-8), 2.94 (1H, qdd, *J* = 6.8, 5.2, 3.2 Hz, H-10), 1.63-1.59 (2H, m, H-6'), 1.48-1.42 (1H, m, H-4'), 1.27-1.23 (2H, m, 5'), 1.22-1.17 (2H, m, 3'), 1.04 (3H, d, *J* = 7.2 Hz, Me-8), 0.88 (9H, s, Si(CH₃)₃), 0.88 (3H, d, *J* = 6.8 Hz, Me-10), 0.79 (3H, d, *J* = 6.4 Hz, Me-4'), 0.04 (6H, s, Si(CH₃)₂).

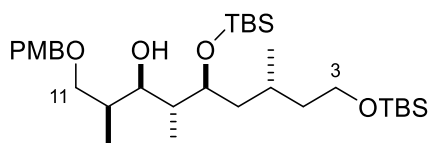
***tert*-Butyl((*R*)-4-((4*S*,5*S*,6*R*)-6-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-methylbutoxy)dimethylsilane (151)**



To a solution of diol **110** (10 mg, 0.02 mmol, 1.0 equiv.) in CH₂Cl₂ (0.2 mL) were added 2,2-dimethoxypropane (53 μ L, 0.43 mmol, 20 equiv.) and PPTS (1 crystal). The reaction mixture was stirred for 2.5 h before being concentrated *in vacuo*. The residue was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (9.3 mg, 86%)

R_f 0.41 (4:1 PE/EtOAc); **IR** (thin film, ν_{max} /cm⁻¹): 3670, 2987, 1407, 1394, 1249, 1080, 869; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.25 (2H, d, J = 8.7 Hz, H-Ar), 6.86 (2H, d, J = 8.7 Hz, H-Ar), 4.43 (1H, d, J = 11.8 Hz, CHaH_bAr), 4.39 (1H, d, J = 11.8 Hz, CHaH_bAr), 3.79 (3H, s, ArOCH₃), 3.66 (1H, dd, J = 10.1, 1.7 Hz, H-7), 3.65-3.61 (2H, m, H-11), 3.48 (1H, td, J = 9.5, 3.3 Hz, H-9), 3.43 (1H, t, J = 8.7 Hz, H-3a), 3.26 (1H, dd, J = 8.7, 6.3 Hz, H-3b), 2.06-2.00 (1H, m, H-10), 1.86-1.77 (1H, m, H-8), 1.54-1.32 (5H, m, H-4, H-5, H-6), 1.36 (3H, s, H-1'), 1.29 (3H, s, H-2'), 0.88 (9H, s, Si(CH₃)₃), 0.84 (3H, d, J = 6.1 Hz, Me-), 0.83 (3H, d, J = 6.4 Hz, Me-), 0.70 (3H, d, J = 6.7 Hz, Me-), 0.03 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 159.1, 131.0, 129.2, 113.7, 97.6, 77.2, 73.2, 73.0, 72.8, 71.9, 61.5, 5.3, 41.0, 40.8, 35.7, 34.0, 30.1, 26.0, 25.4, 19.5, 18.9, 18.3, 11.7, 9.6, -5.2, -5.3.

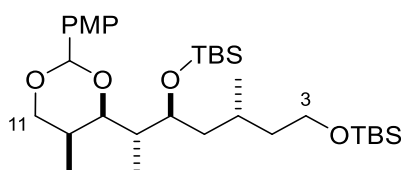
(5*S*,7*R*)-5-((1*R*)-1-((4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethyl)-2,2,3,3,7,11,11,12,12-nonamethyl-4,10-dioxo-3,11-disilatridecane (156)



To a solution of aldol adduct **110** (4.6 g, 10.0 mmol, 1.0 equiv.) in CH₂Cl₂ (100 mL) at -78 °C was added 2,6-lutidine (1.4 mL, 12.1 mmol, 1.2 equiv.) and TBSOTf (2.46 mL, 10.6 mmol, 1.05 equiv.) and stirred for 3 h before quenching with NH₄Cl (50 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were dried over MgSO₄ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (4.93 g, 88%)

R_f 0.24 (9:1 PE/EtOAc); $[\alpha]_D^{20} - 17.4$ (c 1.25, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3691, 1514, 1463, 1250, 1088, 835, 773; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} : 7.24 (2H, d, $J = 8.6$ Hz, H-Ar), 6.87 (2H, d, $J = 8.6$ Hz, H-Ar), 4.47 (1H, d, $J = 11.7$ Hz, $\text{OCH}_a\text{H}_b\text{Ar}$), 4.40 (1H, d, $J = 11.7$ Hz, $\text{OCH}_a\text{H}_b\text{Ar}$), 4.10 (1H, ddd, $J = 9.7, 4.1, 2.4$ Hz, H-7), 3.80 (3H, s, ArOCH_3), 3.67-3.63 (2H, m, H-3a, H-3b), 3.55 (1H, dd, $J = 10.5, 2.5$ Hz, H-9), 3.53 (1H, dd, $J = 9.0, 4.4$ Hz, H-11a), 3.51 (1H, dd, $J = 9.0, 5.1$ Hz, H-11b), 2.71 (1H, d, $J = 2.6$ Hz, O-H), 1.87-1.81 (1H, m, H-10), 1.80-1.70 (2H, m, H-8, H-5), 1.56-1.49 (1H, m, H-4a), 1.43-1.34 (2H, m, H-6a, H-4b), 1.10 (1H, ddd, $J = 12.9, 10.6, 2.2$ Hz, H-6b), 0.93 (3H, d, $J = 7.1$ Hz, Me-10), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.88 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.88 (3H, d, $J = 7.0$ Hz, Me-8), 0.75 (3H, d, $J = 7.0$ Hz, Me-5), 0.06 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CH}_b)_3$), 0.05 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CH}_b)_3$), 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 159.2, 130.3, 129.2, 113.8, 75.3, 75.2, 73.1, 70.5, 61.5, 55.3, 41.8, 41.4, 39.1, 34.9, 26.0, 26.0, 25.7, 19.1, 18.4, 18.1, 10.3, 9.1, -4.2, -4.5, -5.3; HRMS (ES+): calc. for $\text{C}_{32}\text{H}_{62}\text{O}_5\text{Si}_2$ $[\text{M}+\text{H}]^+$ 583.4209, found 583.4195.

(5S,7R)-5-((1R)-1-((4R,5S)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethyl)-2,2,3,3,7,11,11,12,12-nonamethyl-4,10-dioxo-3,11-disilatriscane (109)



Procedure A:

To a solution of alcohol **156** (20 mg, 0.054 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at -78°C were added 2,6-lutidine (29 μL , 0.27 mmol, 5.0 equiv.) and TBSOTf (37 μL , 0.16 mmol, 3.0 equiv.) The reaction mixture was stirred for 30 min at this temperature before being warmed to rt and stirred for a further 1 h. The reaction was then quenched with NH_4Cl (1 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL), combined organic layers dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 PE/EtOAc) to give the title compound as a colourless oil (17.0 mg, 68%)

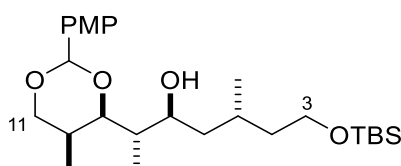
Procedure B:

To a slurry of DDQ (754 mg, 3.31 mmol, 1.1 equiv.) and 4Å MS (525 mg), in CH_2Cl_2 (20 mL) at 0°C was added a solution of PMB ether **157** (1.75 g, 3.01 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 h before being filtered through Celite® and washed with CH_2Cl_2 (15 mL). The filtrate was washed with NaHCO_3 (2 x 20 mL) and back extracted with CH_2Cl_2 (3 x 30 mL). Combined

organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (15:1 \rightarrow 9:1 PE/EtOAc) to give the title compound as a colourless oil (1.40 g, 80%).

R_f 0.38 (6:1 PE/EtOAc); $[\alpha]_D^{20} - 21.6$ (c 0.31, CHCl_3); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1618, 1518, 1463, 1388, 1249, 1103, 833, 773; **¹H NMR** (500 MHz, CDCl_3): δ_{H} 7.38 (2H, d, $J = 8.7$ Hz, H-Ar), 6.87 (2H, d, $J = 8.7$ Hz, H-Ar), 5.37 (1H, s, CHAr), 4.19 (1H, ddd, $J = 10.1, 3.1, 1.7$ Hz, H-7), 4.05 (1H, dd, $J = 11.1, 2.2$ Hz, H-11a), 4.01 (1H, dd, $J = 11.1, 1.1$ Hz, H-11b), 3.81 (3H, s, ArOCH_3), 3.65-3.61 (2H, m, H-3), 3.58 (1H, dd, $J = 10.7, 2.1$ Hz, H-9), 1.95 (1H, dqd, $J = 10.7, 7.0, 3.1$ Hz, H-8), 1.71 (1H, qddd, $J = 6.8, 2.2, 2.1, 1.1$ Hz, H-10), 1.6-1.26 (5H, m, H-4-6), 1.15 (3H, d, $J = 6.8$ Hz, Me-5), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.88 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.79 (3H, d, $J = 7.0$ Hz, Me-8), 0.76 (3H, d, $J = 6.6$ Hz, Me-10), 0.04 (3H, s, $\text{Si}(\text{CH}_3)_3$), 0.04 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.02 (3H, s, $\text{Si}(\text{CH}_3)_3$); **¹³C NMR** (125 MHz, CDCl_3): δ_{C} 159.7, 131.7, 127.1, 113.4, 101.2, 81.2, 74.1, 68.6, 61.5, 55.3, 41.4, 40.4, 38.3, 29.9, 26.0, 26.0, 25.9, 19.0, 18.4, 18.1, 10.9, 7.9, -4.2, -4.6, -5.3, -5.3; **HRMS** (ES⁺): calc. for $\text{C}_{32}\text{H}_{60}\text{O}_5\text{Si}_2$ $[\text{M}+\text{H}]^+$ 581.4052, found 581.4044.

(2S,3S,5R)-7-((tert-Butyldimethylsilyl)oxy)-2-((4R,5S)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-5-methylheptan-3-ol (157)

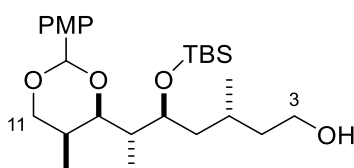


DDQ (24.4 mg, 0.107 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (0.5 mL) and stirred over 4Å MS for 20 min before cooling to 0 °C. A solution of diol **110** (50 mg, 0.107 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) was then added and the reaction mixture stirred for 1 h. The reaction was quenched by filtration through Celite®, which was washed with CH_2Cl_2 (3 mL). The filtrate was washed with NaHCO_3 (3 x 3 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (31.5 mg, 63%).

R_f 0.38 (9:1 PE/EtOAc); $[\alpha]_D^{20} - 20.7$ (c 1.20, CHCl_3); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3671, 2960, 2902, 1616, 1518, 1463, 1394, 1249, 1162, 1070, 893, 832, 775; **¹H NMR** (500 MHz, CDCl_3): δ_{H} 7.38 (2H, d, $J = 8.6$ Hz, H-Ar), 6.87 (2H, d, $J = 8.6$ Hz, H-Ar), 5.47 (1H, s, CHAr), 4.08 (1H, d, $J = 11.2$ Hz, H-11a), 4.03 (1H, d, $J = 11.2$ Hz, H-11b), 3.84 (1H, d, $J = 6.4$ Hz, H-3a), 3.80 (1H, d, $J = 6.4$ Hz, H-3b), 3.79 (3H, s, ArOCH_3), 3.65 (2H, td, $J =$ Hz, H-7), 3.36 (1H, dd, $J = 9.0, 6.7$ Hz, H-9), 1.88-1.78 (2H, m, H-10, H-8), 1.72-1.66 (1H, m, H-6a), 1.57-1.24 (4H, m, H-4, H-5, H-6b), 1.21 (3H, d, $J = 6.9$ Hz, Me-5), 0.89 (3H, d, $J = 6.0$ Hz, Me-

8), 0.88 (9H, s, SiC(CH₃)₃), 0.78 (3H, d, *J* = 6.7 Hz, Me-10), 0.04 (6H, s, Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃): δ_c 159.7, 131.6, 128.0, 113.6, 102.3, 75.1, 73.8, 68.8, 61.4, 55.2, 42.3, 41.5, 41.1, 38.1, 34.8, 26.1, 25.5, 19.6, 12.7, 8.9, – 5.3.

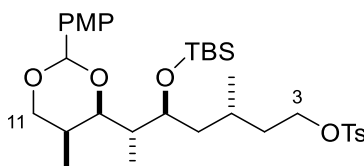
(3*R*,5*S*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-methylheptan-1-ol (183)



To a solution of silyl ether **109** (3.70 g, 6.38 mmol, 1.0 equiv.) in THF (100 mL) at rt was added TBAF (1M in THF, 6.4 mL, 6.38 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred for 1 h before the addition of an extra 0.5 equiv. of TBAF. After a further h, the reaction was quenched with NH₄Cl (50 mL) and the layers separated. The aqueous layer was extracted with Et₂O (3 x 30 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 PE/EtOAc) to give the title compound (2.52 g, 85%), plus silyl ether **109** (390 mg, 11%)

R_f 0.16 (6:1 PE/EtOAc); [α]_D²⁰ – 22.2 (*c* 0.6, CHCl₃); **IR** (thin film, ν_{max}/cm^{–1}): 3363, 1380, 1086, 1045, 880, 772; **¹H NMR** (500 MHz, CDCl₃): δ_H 7.38 (2H, d, *J* = 8.6 Hz, H-Ar), 6.88 (2H, d, *J* = 8.6 Hz, H-Ar), 5.38 (1H, s, CHAr), 4.19 (1H, ddd, *J* = 10.2, 3.6, 1.8 Hz, H-7), 4.06 (1H, dd, *J* = 11.0, 2.3 Hz, H-11a), 4.02 (1H, dd, *J* = 11.1, 1.3 Hz, H-11b), 3.81 (3H, s, OCH₃), 3.71–3.64 (2H, m, H-3), 3.58 (1H, dd, *J* = 10.6, 2.1 Hz, H-9), 1.97 (1H, dqd, *J* = 10.6, 7.0, 3.6 Hz, H-8), 1.70 (1H, qddd, *J* = 6.8, 2.3, 2.1, 1.3 Hz, H-10), 1.61–1.47 (2H, m, H-5, H-4a), 1.43 (1H, ddd, *J* = 12.8, 10.2, 2.6 Hz, H-6a), 1.28–1.24 (1H, m, H-4b), 1.15 (3H, d, *J* = 6.9 Hz, Me-5), 1.05 (1H, ddd, *J* = 12.8, 10.2, 1.8 Hz, H-6b), 0.89 (9H, s, SiC(CH₃)₃), 0.80 (3H, d, *J* = 6.8 Hz, Me-10), 0.79 (3H, d, *J* = 7.0 Hz, Me-8), 0.05 (3H, s, Si(CH₃)₂(CHb₃)), 0.03 (3H, s, Si(CH₃)₂(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_c 159.7, 131.6, 127.1, 113.4, 101.2, 81.2, 74.1, 68.9, 61.2, 55.3, 41.0, 40.4, 37.8, 29.9, 26.0, 25.9, 19.6, 18.1, 10.9, 7.9, – 4.2, – 4.6; **HRMS** (ES⁺): calc. for C₂₆H₄₇O₄Si [M+H]⁺ 467.3187, found 467.3184.

(3*R*,5*S*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-methylheptyl 4-methylbenzenesulfonate (184)



To a solution of alcohol **183** (420 mg, 0.91 mmol, 1.0 equiv.) in CH₂Cl₂/pyridine (1:1, 10 mL), was added tosyl chloride (516 mg, 2.72 mmol 3.0 equiv.) and stirred for 6 h. The reaction was then quenched with NaHCO₃ (12 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 8 mL), combined organic layers dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (15:1 PE/EtOAc) to give the title compound as a colourless oil (510 mg, 91%).

Major diastereomer:

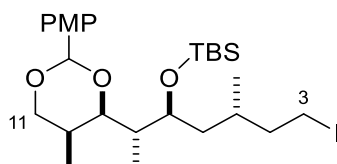
R_f 0.28 (6:1 PE/EtOAc); $[\alpha]_D^{20}$ – 7.0 (*c* 0.1, CHCl₃); **IR** (thin film, ν_{\max} /cm^{–1}): 2927, 2339, 2012, 1613, 1360, 1249, 1177, 1073, 942, 828, 773; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.78 (2H, d, *J* = 8.3 Hz, H-Ar), 7.36 (2H, d, *J* = 8.8 Hz, H-Ar), 7.32 (2H, d, *J* = 8.3 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 5.35 (1H, CHAr), 4.14 (1H, ddd, *J* = 9.8, 3.4, 1.8 Hz, H-7), 4.09–4.02 (4H, m, H-11, H-3), 3.80 (3H, s, ArOCH₃), 3.53 (1H, dd, *J* = 10.7, 2.1 Hz, H-9), 2.44 (3H, s, ArCH₃), 1.98–1.91 (1H, m, H-10), 1.69–1.62 (1H, m, H-8), 1.60–1.24 (5H, m, H-4–6), 1.14 (3H, d, *J* = 6.8 Hz, Me-8), 0.86 (9H, s, SiC(CH₃)₃), 0.76 (3H, d, *J* = 7.1 Hz, Me-10), 0.71 (3H, d, *J* = 6.4 Hz, Me-5), 0.03 (3H, s, Si(CH₃)₃(CHb₃)), – 0.01 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 159.7, 144.6, 133.3, 131.6, 129.8, 127.9, 127.0, 113.4, 101.2, 81.2, 74.1, 69.0, 68.4, 55.3, 40.3, 37.7, 36.9, 29.8, 25.9, 25.8, 21.6, 18.7, 18.1, 10.9, 7.9, –4.2, –4.7; **HRMS** (ES⁺): calc. for C₃₃H₅₃O₇SSi [M+H]⁺ 621.3281, found 621.3269.

Minor diastereomer:

¹H NMR (500 MHz, CDCl₃): δ_{H} 7.79 (2H, d, 8.1 Hz, H-Ar), 7.36 (2H, d, *J* = 8.8 Hz, H-Ar), 7.33 (2H, d, *J* = 8.1 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 5.99 (1H, s, CHAr), 4.27 (1H, dt, *J* = 11.4, 2.7 Hz, H-7), 4.09–4.02 (2H, m, H-3), 4.01 (1H, dd, *J* = 11.1, 1.2 Hz, H-11a), 3.82 (3H, s, ArOCH₃), 3.62 (1H, dd, *J* = 11.1, 2.4 Hz, H-11b), 3.40 (1H, dd, *J* = 10.6, 2.2 Hz, H-9), 2.44 (3H, s, ArCH₃), 1.98–1.91 (1H, m, H-10), 1.69–1.62 (1H, m, H-8), 1.60–1.24 (5H, m, H-4–6), 1.16 (3H, d, *J* = 7.1 Hz, Me-8), 0.88 (9H, s, SiC(CH₃)₃), 0.95 (3H,

d, $J = 6.7$ Hz, Me-5), 0.66 (3H, d, $J = 7.1$ Hz, Me-10), 0.10 (3H, s, Si(CH₃)(CHb₃)), 0.07 (3H, s, Si(CHa₃)(CHb₃)); ¹³C NMR (125 MHz, CDCl₃): δ_c 159.4, 144.6, 133.3, 131.6, 130.2, 128.2, 127.9, 113.8, 96.5, 81.1, 72.3, 68.1, 67.1, 55.3, 40.9, 37.1, 36.7, 30.7, 25.9, 25.7, 21.6, 18.5, 18.1, 10.9, 8.1, -4.1, -4.6.

tert-Butyl(((2*R*,3*S*,5*S*)-7-iodo-2-((4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-5-methylheptan-3-yl)oxy)dimethylsilane (108)



To a stirred solution of tosylate **184** (500 mg, 0.808 mmol, 1.0 equiv.) in MeCN (20 mL) was added LiI (650 mg, 4.84 mmol, 6.0 equiv.) and heated to 60 °C for 4 h. Upon completion, the reaction mixture was cooled to rt and diluted with Et₂O (15 mL) and quenched with NaHCO₃ (20 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 20 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (10:1 PE/EtOAc) to give the title compound as a colourless oil (425 mg, 91%).

Major diastereomer:

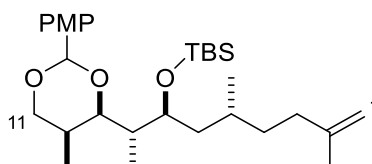
R_f 0.48 (6:1 PE/EtOAc); $[\alpha]_D^{20} - 22.8$ (c 0.82, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1616, 1518, 1463, 1380, 1249, 1164, 1036, 834, 774; ¹H NMR (500 MHz, CDCl₃): δ_H 7.38 (2H, d, $J = 8.7$ Hz, H-Ar), 6.88 (2H, d, $J = 8.7$ Hz, H-Ar), 5.37 (1H, s, CHAr), 4.18 (1H, ddd, $J = 10.1, 3.2, 1.6$ Hz, H-7), 4.07-4.00 (2H, m, H-11), 3.81 (3H, s, ArOCH₃), 3.56 (1H, dd, $J = 10.7, 2.0$ Hz, H-9), 3.27-3.14 (2H, m, H-3), 2.00-1.93 (1H, m, H-10), 1.89-1.80 (1H, m, H-8), 1.74-1.26 (5H, m, H-4, H-5, H-6), 1.15 (3H, d, $J = 6.9$ Hz, Me-5), 0.88 (9H, s, Si(CH₃)₃), 0.79 (3H, d, $J = 7.1$ Hz, Me-10), 0.76 (3H, d, $J = 6.1$ Hz, Me-8), 0.05 (3H, s, Si(CH₃)(CHb₃)), 0.05 (3H, s, Si(CHa₃)(CHb₃)); ¹³C NMR (125 MHz, CDCl₃): δ_c 159.7, 131.6, 127.1, 113.5, 101.2, 81.2, 74.1, 68.5, 55.3, 42.3, 40.4, 37.4, 30.4, 29.9, 26.0, 18.3, 18.1, 10.9, 7.9, 4.9, -4.2, -4.5; **HRMS** (ES⁺): calc. for C₂₆H₄₆IO₄Si [M+H]⁺ 577.2205, found 577.2196.

Minor diastereomer:

¹H NMR (500 MHz, CDCl₃): δ_H 7.35 (2H, d, $J = 8.7$ Hz, H-Ar), 6.89 (2H, d, $J = 8.7$ Hz, H-Ar), 6.01 (1H, s, CHAr), 4.31 (1H, ddd, $J = 11.5, 2.8, 2.0$ Hz, H-7), 4.07-4.00 (2H, m, H-11a), 3.83 (3H, s, ArOCH₃), 3.62 (1H, dd, $J = 11.2, 2.3$ Hz, H-9), 3.44 (1H, dd, $J = 10.7, 2.4$ Hz, H-11b), 3.27-3.14 (2H, m, H-3), 2.00-1.93 (1H, m, H-10), 1.89-1.80 (1H, m, H-8), 1.74-1.26 (5H, m, H-4, H-5, H-6), 1.17 (3H, d, $J = 6.9$ Hz, Me-5),

1.00 (3H, d, J = 6.6 Hz, Me-8), 0.88 (9H, s, Si(CH₃)₃), 0.71 (3H, d, J = 7.0 Hz, Me-10), 0.12 (6H, s, Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃): δ_c 159.4, 130.3, 128.3, 113.8, 96.5, 72.3, 68.1, 67.1, 55.3, 42.5, 41.0, 36.3, 30.7, 30.3, 26.0, 22.6, 20.5, 18.2, 17.9, 11.5, -4.0

***tert*-Butyl(((2*R*,3*S*,5*R*)-2-((4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-5,8-dimethylnon-8-en-3-yl)oxy)dimethylsilane (**104**)**



A solution of iodide **108** (400 mg, 0.69 mmol, 1.0 equiv.) in Et₂O (7 mL) was cooled to -78 °C and *t*-BuLi (1.7 M in pentane, 1.6 mL, 2.78 mmol, 4.0 equiv.) added in a single portion. The reaction mixture was stirred for 3 min before the addition of B-Methoxy-9-BBN (1 M in hexanes, 4.27 mL, 4.27 mmol, 6.0 equiv.). After a further 5 min, the THF (7 mL) was added and the resulting solution slowly warmed to rt and stirred for a further h. K₃PO₄ (3M, 0.7 mL, 2.01 mmol, 3.0 equiv.), Pd(dppf)Cl₂ (51 mg, 0.069 mmol, 0.1 equiv.) and DMF (7 mL) were then added, followed by 2-bromopropene (0.18 mL, 2.07 mmol, 3.0 equiv.) The resulting solution was stirred for 16 h before being quenched with H₂O (20 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 15 mL). Combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 20:1 PE/EtOAc) to give the title compound as pale-yellow oil (231 mg, 67%) in an inseparable 3:1 mixture with alkane **185**.

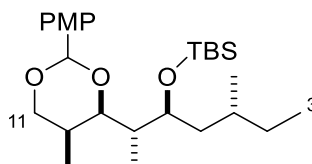
Major diastereomer:

R_f 0.58 (9:1 PE/EtOAc); [α]_D²⁰ - 41.6 (*c* 0.37, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 2336, 1616, 1518, 1463, 1249, 1072, 833, 773; ¹H NMR (500 MHz, CDCl₃): δ_H 7.37 (2H, d, J = 8.6 Hz, H-Ar), 6.86 (2H, d, J = 8.6 Hz, H-Ar), 5.36 (1H, s, CH₂Ar), 4.66-4.63 (2H, m, H-2), 4.17 (1H, ddd, J = 10.1, 3.2, 1.7 Hz, H-7), 4.04 (1H, dd, J = 11.2, 2.4 Hz, H-11a), 4.00 (1H, dd, J = 11.2, 1.2 Hz, H-11b), 3.79 (3H, s, ArOCH₃), 3.57 (1H, dd, J = 10.8, 2.0 Hz, H-9), 1.96-1.91 (1H, m, H-8), 1.84-1.78 (1H, m, H-10), 1.69 (3H, s, Me-2), 1.64-1.25 (7H, m, H-3, H-4, H-5, H-6), 1.13 (3H, d, J = 6.9 Hz, Me-5), 0.87 (9H, s, Si(CH₃)₃), 0.78 (3H, d, J = 7.0 Hz, Me-8), 0.76 (3H, d, J = 6.6 Hz, Me-10), 0.03 (3H, s, Si(CH₃)₂(CH₃)), 0.00 (3H, s, Si(CH₃)₂(CH₃)); ¹³C NMR (125 MHz, CDCl₃): δ_c 159.7, 146.5, 131.7, 127.1, 113.4, 109.5, 101.2, 81.2, 74.1, 68.7, 55.3, 40.5, 38.0, 36.4, 35.4, 29.9, 28.7, 25.9, 22.5, 19.1, 18.1, 10.9, 7.9, -4.2, -4.7; **HRMS** (ES⁺): calc. for C₂₉H₅₁O₄Si [M+H]⁺ 491.3551, found 491.3542.

Minor diastereomer:

¹H NMR (500 MHz, CDCl₃): δ_H 7.35 (2H, d, *J* = 8.7 Hz, H-Ar), 6.88 (2H, d, *J* = 8.7 Hz, H-Ar), 6.00 (1H, s, CHAr), 4.67-4.65 (2H, m, H-1), 4.30 (1H, ddd, *J* = 11.6, 2.7, 2.1 Hz, H-7), 4.00 (1H, dd, *J* = 11.2, 1.2 Hz, H-11a), 3.81 (3H, s, ArOCH₃), 3.61 (1H, dd, *J* = 11.2, 2.2 Hz, H-11b), 3.44 (1H, dd, *J* = 10.6, 2.5 Hz, H-9), 1.96-1.91 (1H, m, H-8), 1.84-1.78 (1H, m, H-10), 1.70 (3H, s, Me-2), 1.64-1.25 (7H, m, H-3, H-4, H-5, H-6), 1.16 (3H, d, *J* = 6.9 Hz, Me-5), 1.00 (3H, d, *J* = 6.8 Hz, Me-10), 0.89 (9H, s, Si(CH₃)₃), 0.70 (3H, d, *J* = 7.1 Hz, Me-8), 0.10 (3H, s, Si(CH₃)₃(CHb₃)), 0.08 (3H, s, Si(CH₃)₃(CHb₃)).

tert-Butyl(((2*R*,3*S*,5*R*)-2-((4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-5-methylheptan-3-yl)oxy)dimethylsilane (185)



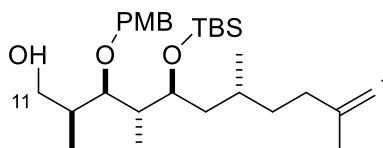
Major diastereomer:

R_f 0.58 (9:1 PE/EtOAc); [α]_D²⁰ -2.8 (c 0.12, CHCl₃); **IR** (thin film, ν_{max}/cm⁻¹): 1380, 1258, 1169, 1023, 834, 776; **¹H NMR** (400 MHz, CDCl₃): δ_H 7.39 (2H, d, *J* = 8.8 Hz, H-Ar), 6.88 (2H, d, *J* = 8.8 Hz, H-Ar), 5.38 (1H, s, CHAr), 4.18 (1H, ddd, *J* = 9.9, 3.3, 1.9 Hz, H-7), 4.07-4.00 (2H, m, H-11), 3.81 (3H, s, ArOCH₃), 3.59 (1H, dd, *J* = 10.7, 2.1 Hz, H-9), 2.00-1.91 (1H, m, H-10), 1.63-1.57 (1H, m, H-8), 1.48-1.22 (8H, m, H-3, H-4, H-5, H-6), 1.16 (3H, d, *J* = 7.0 Hz, Me-8), 0.89 (9H, s, Si(CH₃)₃), 0.80 (3H, d, *J* = 6.4 Hz, Me-5), 0.75 (3H, d, *J* = 7.0 Hz, Me-10), 0.05 (3H, s, Si(CH₃)₃(CHb₃)), 0.03 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_C 159.5, 131.6, 126.9, 113.3, 101.1, 81.1, 74.0, 68.7, 55.1, 40.4, 37.5, 30.8, 30.6, 29.8, 25.8, 18.7, 18.0, 11.5, 10.8, 7.8, -4.3, -4.7; **HRMS** (ES⁺): calc. for C₂₆H₄₇O₄Si [M+H]⁺ 451.3233, found 451.3238.

Minor diastereomer:

¹H NMR (400 MHz, CDCl₃): δ_H 7.37 (2H, d, *J* = 8.8 Hz, H-Ar), 6.90 (2H, d, *J* = 8.8 Hz, H-Ar), 6.02 (1H, s, CHAr), 4.32 (1H, dt, *J* = 11.1, 2.6 Hz, H-7), 4.07-4.00 (2H, m, H-11), 3.82 (3H, s, ArOCH₃), 3.62 (1H, dd, *J* = 11.2, 2.3 Hz, H-9), 2.00-1.91 (1H, m, H-10), 1.63-1.57 (1H, m, H-8), 1.48-1.22 (7H, m, H-3, H-4, H-5, H-6), 1.18 (3H, d, *J* = 7.0 Hz, Me-8), 0.91 (9H, s, Si(CH₃)₃), 0.71 (3H, d, *J* = 7.1 Hz, Me-10), 0.13 (3H, s, Si(CH₃)₃(CHb₃)), 0.11 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_C 159.2, 130.1, 128.2, 113.7, 96.4, 72.3, 58.3, 66.9, 55.2, 41.0, 36.4, 31.0, 30.6, 30.2, 25.9, 18.3, 18.1, 11.4, 10.8, 8.0, -4.2, -4.7.

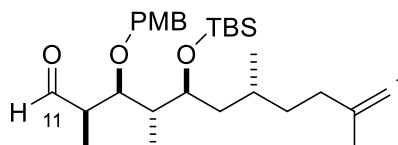
(2S,3R,4R,5S,7R)-5-((tert-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4,7,10-tetramethylundec-10-en-1-ol (193)



To a solution of PMP acetal **104** (170 mg, 0.347 mmol, 1.0 equiv.) in CH_2Cl_2 (3.5 mL) at -78°C was added DIBAL (1 M in hexanes, 1.7 mL, 1.735 mmol, 5.0 equiv.) dropwise. The reaction mixture was stirred for 1 h at this temperature and then warmed to rt over another h. Upon completion, the reaction was quenched with NaK tartrate (5 mL) and stirred for 2 h before the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), combined organic layers dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc), to give the title compound as a colourless oil (140 mg, 82%).

R_f 0.14 (9:1 PE/EtOAc); $[\alpha]_D^{20} - 23.6$ (c 2.50, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3377, 1614, 1514, 1462, 1378, 1240, 1037, 834, 773; ^1H NMR (500 MHz, CDCl_3): δ_{H} 7.25 (2H, d, $J = 8.9$ Hz, H-Ar), 6.87 (2H, d, $J = 8.9$ Hz, H-Ar), 4.68 (1H, app s, H-1), 4.67 (1H, app s, H-1), 4.53 (1H, d, $J = 10.9$ Hz, CHaCHbAr), 4.49 (1H, d, $J = 10.9$ Hz, CHaHbAr), 4.18 (1H, dt, $J = 11.0, 2.5$ Hz, H-7), 3.80 (3H, s, ArOCH_3), 3.65-3.59 (2H, m, H-11), 3.42 (1H, dd, $J = 10.2, 1.8$ Hz, H-9), 2.03-1.98 (1H, m, H-10), 1.95-1.89 (1H, m, H-8), 1.72 (3H, s, Me-2), 1.66-1.10 (8H, m, H-3-6, O-H), 0.88 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.88 (3H, d, $J = 6.8$ Hz, Me-10), 0.85 (3H, d, $J = 6.6$ Hz, Me-8), 0.82 (3H, d, $J = 7.0$ Hz, Me-5), 0.05 (3H, s, $\text{Si}(\text{CH}_3)_2(\text{CHb}_3)$), 0.02 (3H, s, $\text{Si}(\text{CH}_3)_2(\text{CHb}_3)$); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 158.9, 146.4, 131.2, 128.6, 113.7, 109.6, 80.6, 73.6, 69.6, 66.1, 55.3, 42.6, 38.3, 37.8, 36.4, 35.3, 31.0, 28.6, 25.9, 22.6, 19.1, 18.1, 9.9, -4.1 , -4.6 .

(2R,3S,4R,5S,7R)-5-((tert-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4,7,10-tetramethylundec-10-enal (194)

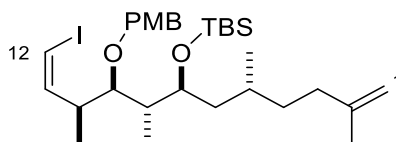


To a solution of alcohol **193** (130 mg, 0.26 mmol, 1.0 equiv.) in CH_2Cl_2 (2.6 mL) were added triacetoxyiodobenzene (568 mg, 1.32 mmol, 5.0 equiv.) and anhydrous NaHCO_3 (178 mg, 2.11 mmol, 8.0 equiv.) and stirred for 20 min. The reaction was then quenched with NaHCO_3 (2 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL) and stirred for a further 10 min before the layers were separated. The aqueous layer was

extracted with CH_2Cl_2 (3 x 4 mL), combined organic layers dried over MgSO_4 and concentrated *in vacuo*. The crude material (95 mg, 73%), was used without further purification.

R_f 0.39 (9:1 PE/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 9.84 (1H, d, $J = 1.6$ Hz, H-11), 7.17 (2H, d, $J = 8.7$ Hz, H-Ar), 6.84 (2H, d, $J = 8.7$ Hz, H-Ar), 4.69-4.66 (2H, m, H-1), 4.26 (2H, s, CH_2Ar), 4.17 (1H, ddd, $J = 11.2, 3.1, 2.3$ Hz, H-7), 3.83-3.79 (4H, m, ArOCH_3 , H-10), 2.52 (1H, qd, $J = 7.2, 1.6$ Hz, H-10), 2.02-1.96 (1H, m, H-8), 1.72 (3H, s, Me-2), 1.64-1.28 (7H, m, H-3, H-4, H-5, H-6), 1.18 (3H, d, $J = 7.1$ Hz, Me-10), 0.88 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.87 (3H, d, $J = 6.7$ Hz, Me-8), 0.82 (3H, d, $J = 6.6$ Hz, Me-5), 0.03 (3H, s, $\text{Si}(\text{CH}_3)_3$), 0.01 (3H, s, $\text{Si}(\text{CH}_3)_3$).

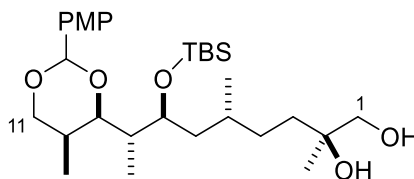
***tert*-Butyl(((3*S*,4*R*,5*R*,6*S*,8*R*,*Z*)-1-iodo-4-((4-methoxybenzyl)oxy)-3,5,8,11-tetramethyldodeca-1,11-dien-6-yl)oxy)dimethylsilane (186)**



To a suspension of (iodomethane)triphenylphosphonium iodide (288 mg, 0.55 mmol, 3.0 equiv.) in THF (1.3 mL) at 0 °C was added NaHMDS (1 M in THF, 0.55 mL, 0.55 mmol, 3.0 equiv.) and stirred for 30 min before being cooled to -78 °C. A solution of aldehyde **194** (90 mg, 0.18 mmol, 1.0 equiv.) in THF (0.5 mL) was added *via* cannula and the reaction mixture stirred for a further 90 min before being quenched with PE (3 mL) and filtered through Celite®. The filtrate was then dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give the title compound as a colourless oil (99 mg, 88%).

R_f 0.64 (9:1 PE/EtOAc); $[\alpha]_D^{20} + 55.4$ (c 1.00, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1514, 1462, 1248, 1065, 834, 773; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_H 7.22 (2H, d, $J = 8.6$ Hz, H-Ar), 6.86 (2H, d, $J = 8.6$ Hz, H-Ar), 6.22 (1H, dd, $J = 8.6, 7.3$ Hz, H-11), 6.16 (1H, dd, $J = 7.3, 1.5$ Hz, H-12), 4.68-4.66 (2H, m, H-1), 4.46 (1H, d, $J = 11.0$ Hz, CHaCHbAr), 4.42 (1H, d, $J = 11.0$ Hz, CHaCHbAr), 4.11 (1H, ddd, $J = 10.4, 3.2, 1.8$ Hz, H-), 3.80 (3H, s, ArOCH_3), 3.25 (1H, dd, $J = 9.6, 2.9$ Hz, H-), 2.72 (1H, dqd, $J = 8.6, 6.8, 2.9$ Hz, H-10), 1.98-1.91 (1H, m, H-8), 1.71 (3H, s, Me-2), 1.63-1.06 (7H, m, H-3, H-4, H-5, H-6), 1.04 (3H, d, $J = 6.8$ Hz, Me-10), 0.92 (3H, d, $J = 7.1$ Hz, Me-8), 0.88 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.83 (3H, d, $J = 6.6$ Hz, Me-5), 0.03 (3H, s, $\text{Si}(\text{CH}_3)_3$), 0.01 (3H, s, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_C 158.9, 146.4, 145.4, 131.2, 128.4, 113.6, 109.5, 83.4, 80.9, 74.1, 69.5, 55.3, 55.3, 42.8, 41.8, 38.6, 36.4, 35.3, 28.6, 26.0, 22.5, 19.1, 18.1, 12.4, 10.4, $-4.1, -4.6$; HRMS (ES⁺): calc. for $\text{C}_{30}\text{H}_{52}\text{IO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 615.2721, found 615.2725.

(2*S*,5*R*,7*S*,8*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-((4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-2,5-dimethylnonane-1,2-diol (197)



To a solution of alkene **104** (50 mg, 0.102 mmol, 1.0 equiv.) (as a 3:1 mixture with alkane **185**), in *t*-BuOH/H₂O (1:1, 1 mL), were added K₂OsO₂(OH)₄ (0.74 mg, 2 μmol, 2.0 mol%), (DHQ)₂AQN (2.3 mg, 3 μmol, 3.0 mol%), K₂CO₃ (42.5 mg, 0.306 mmol, 3.0 equiv.) and K₃Fe(CN)₆ (101 mg, 0.306 mmol, 3.0 equiv.) and stirred for 16 h. The reaction was quenched with Na₂S₂O₃ (2 mL) and Et₂O (2 mL) before the layers were separated. The aqueous layer was extracted with Et₂O (3 x 3 mL) and EtOAc (2 x 3 mL). Combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (3:1 PE/EtOAc) to give the title compound as a viscous colourless oil (25 mg, 63%, 2.3:1 ratio of PMP acetal diastereomers) and alkane **185** (12 mg).

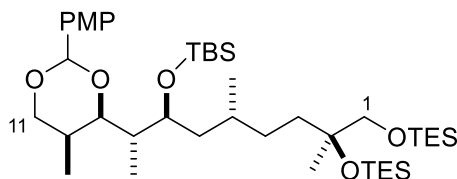
Major diastereomer:

R_f 0.18 (3:1 PE/EtOAc); [α]_D²⁰ – 33.2 (*c* 1.80, CHCl₃); **IR** (thin film, ν_{max} /cm^{–1}): 3466, 3416, 1517, 1463, 1379, 1249, 1166, 1038, 834, 774; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.39 (2H, d, *J* = 8.8 Hz, H-Ar), 6.88 (2H, d, *J* = 8.8 Hz, H-Ar), 5.37 (1H, s, CHAr), 4.20 (1H, ddd, *J* = 10.0, 3.1, 1.5 Hz, H-7), 4.04–4.01 (2H, m, H-11), 3.81 (3H, s, ArOCH₃), 3.58 (1H, dd, *J* = 10.3, 2.0 Hz, H-9), 3.45 (1H, d, *J* = 10.7 Hz, H-1a), 3.39 (1H, d, *J* = 10.7 Hz, H-1b), 2.04 (1H, br s, O-H), 2.00–1.93 (1H, m, H-10), 1.86 (1H, br s, O-H), 1.61–1.57 (1H, m, H-8), 1.55–1.22 (7H, m, H-3–6), 1.16 (3H, d, *J* = 7.0 Hz, Me-8), 1.15 (3H, s, Me-2), 0.89 (9H, s, Si(CH₃)₃), 0.79 (3H, d, *J* = 6.4 Hz, Me-5), 0.80 (3H, d, *J* = 7.0 Hz, Me-10), 0.05 (3H, s, Si(CH₃)₃), 0.03 (3H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 159.7, 131.6, 127.1, 113.5, 101.2, 81.3, 74.1, 73.0, 69.9, 68.7, 55.3, 40.5, 37.7, 36.2, 32.1, 29.9, 29.4, 25.9, 23.3, 19.2, 18.1, 10.9, 7.9, –4.2, –4.6; **HRMS** (ES⁺): calc. for C₂₉H₅₃O₆Si [M+H]⁺ 525.3611, found 525.3612.

Minor diastereomer:

¹H NMR (500 MHz, CDCl₃): δ_{H} 7.39 (2H, d, *J* = 8.8 Hz, H-Ar), 6.90 (2H, d, *J* = 8.8 Hz, H-Ar), 6.02 (1H, s, CHAr), 4.32 (1H, dt, *J* = 11.5, 2.1 Hz, H-7), 4.04–4.01 (2H, m, H-11), 3.83 (3H, s, ArOCH₃), 3.63 (1H, dd, *J* = 11.3, 2.1 Hz, H-9), 3.45 (1H, d, *J* = 10.7 Hz, H-1a), 3.39 (1H, d, *J* = 10.7 Hz, H-1b), 2.04 (1H, br s, O-H), 2.00–1.93 (1H, m, H-10), 1.88 (1H, br s, O-H), 1.18 (3H, d, *J* = 7.0 Hz, Me-8), 1.55–1.22 (7H, m, H-3–6), 1.15 (3H, s, Me-2), 0.91 (9H, s, Si(CH₃)₃), 0.71 (3H, d, *J* = 7.1 Hz, Me-10), 0.13 (3H, s, Si(CH₃)₃), 0.11 (3H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 159.3, 130.3, 128.3, 113.9, 96.6, 81.2, 72.4, 68.2, 67.1, 65.9, 55.3, 41.1, 37.8, 36.1, 32.4, 30.7, 30.3, 23.3, 18.9, 18.2, 15.3, 10.9, 8.1, –4.1, –4.6.

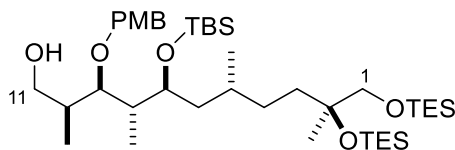
(5S,7R,10S)-13,13-Diethyl-5-((1R)-1-((4R,5S)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethyl)-2,2,3,3,7,10-hexamethyl-10-((triethylsilyl)oxy)-4,12-dioxo-3,13-disilapentadecane (198)



To a solution of diol **197** (22 mg, 0.038 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at -78°C were added 2,6-lutidine (49 μL , 0.478 mmol, 12.5 equiv.) and TESOTf (53 μL , 0.288 mmol, 7.5 equiv.) and stirred for 1 h before being warmed up to rt. After stirring for a further 30 min, the reaction was quenched with NH_4Cl (1 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 1 mL), combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE \rightarrow 10:1 PE/EtOAc) to give the title compound as a colourless oil (31 mg, 99%).

R_f 0.61 (3:1 PE/EtOAc); $[\alpha]_D^{20} -12.7$ (c 0.85, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1517, 1461, 1249, 1166, 1106, 1014, 833, 740; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.39 (2H, d, $J = 8.7$ Hz, H-Ar), 6.88 (2H, d, $J = 8.7$ Hz, H-Ar), 5.38 (1H, s, CHAr), 4.17 (1H, br d, $J = 9.8$ Hz, H-7), 4.06 (1H, dd, $J = 11.3, 2.2$ Hz, H-11a), 4.02 (1H, dd, $J = 11.3, 1.1$ Hz, H-11b), 3.81 (3H, s, ArOCH_3), 3.58 (1H, dd, $J = 10.5, 2.0$ Hz, H-9), 3.39 (1H, d, $J = 9.4$ Hz, H-1a), 3.30 (1H, dd, $J = 9.4, 2.0$ Hz, H-1b), 1.95 (1H, qddd, $J = 7.0, 2.2, 2.0, 1.1$ Hz, H-10), 1.61-1.56 (1H, m, H-8), 1.50-1.19 (7H, m, H-3-6), 1.15 (3H, d, $J = 6.8$ Hz, Me-8), 1.14 (3H, s, Me-2), 0.95 (9H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.93 (9H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.88 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.79 (3H, d, $J = 7.0$ Hz, Me-10), 0.75 (3H, d, $J = 6.5$ Hz, Me-5), 0.58 (6H, q, $J = 7.9$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.56 (6H, q, $J = 7.8$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.04 (3H, s, $\text{Si}(\text{CH}_3)_3$), 0.02 (3H, s, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 159.7, 131.7, 127.1, 113.4, 101.2, 81.2, 75.9, 74.1, 69.9, 68.7, 55.3, 40.4, 38.1, 37.1, 31.9, 29.9, 29.5, 25.9, 25.3, 22.6, 19.3, 18.1, 10.9, 7.8, 7.2, 6.8, 4.4, -4.2 , -4.7 ; HRMS (ES $^+$): calc. for $\text{C}_{41}\text{H}_{81}\text{O}_6\text{Si}_3$ $[\text{M}+\text{H}]^+$ 753.5341, found 753.5349.

(2*S*,3*R*,4*R*,5*S*,7*R*,10*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4,7,10-tetramethyl-10,11-bis((triethoxysilyl)oxy)undecan-1-ol (195)



Procedure A:

To a stirred solution of PMP acetal **198** (87 mg, 0.116 mmol, 1.0 equiv.) in CH₂Cl₂ (1.2 mL) at –30 °C was added DIBAL (1 M in hexanes, 0.58 mL, 0.58 mmol, 5.0 equiv.) over 10 min. The reaction mixture was maintained at this temperature for 3 h before being quenched with NaK tartrate (3 mL) and stirred for a further 1 h. The layers were then separated and the aqueous layer extracted with CH₂Cl₂ (3 x 3 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil, (48 mg 58%).

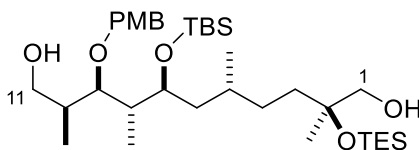
Procedure B:

To a stirred solution of PMP acetal **198** (30.0 mg, 0.039 mmol, 1.0 equiv.) in CH₂Cl₂ (0.6 mL) at –78 °C was added DIBAL (1 M in hexanes, 0.20 mL, 0.20 mmol, 5.0 equiv.) over 10 min. The reaction mixture was maintained at this temperature for 30 min before being warmed to 0 °C over 30 min and stirred for a further 1 h. The reaction was then quenched with NaK tartrate (1 mL) and stirred for 1 h. The layers were then separated and the aqueous layer extracted with CH₂Cl₂ (3 x 3 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil, (11.7 mg, 40%) and diol **199** (10.3 mg, 41 %).

R_f 0.18 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ –28.7 (*c* 1.30, CHCl₃); **IR** (thin film, ν_{\max} /cm^{–1}): 3443, 1614, 1514, 1461, 1248, 1087, 1038, 822, 741; **¹H NMR** (500 MHz, CDCl₃): δ_H 7.26 (2H, d, *J* = 8.8 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 4.53 (1H, d, *J* = 11.0 Hz, CH_AH_BAr), 4.48 (1H, d, *J* = 11.0 Hz, CH_AH_BAr), 4.17 (1H, d, *J* = 10.7 Hz, H-7), 3.80 (3H, s, ArOCH₃), 3.66–3.58 (2H, m, H-11), 3.42 1H, dd, *J* = 10.1, 2.2 Hz, H-9), 3.40 (1H, d, *J* = 10.0 Hz, H-1a), 3.31 (1H, dd, *J* = 9.5, 2.6 Hz, H-1b), 2.04–1.97 (1H, m, H-8), 1.94–1.89 (1H, m, H-10), 1.60 (1H, t, *J* = 5.2 Hz, O-H), 1.53–1.19 (7H, m, H-3, H-4, H-5, H-6), 1.16 (3H, s, Me-2), 0.96 (9H, t, *J* = 8.0 Hz, Si(CH₂CH₃)₃), 0.94 (9H, t, *J* = 7.8 Hz, Si(CH₂CH₃)₃), 0.89 (3H, d, *J* = 7.0 Hz, Me-10), 0.88 (9H, s, Si(CH₃)₃), 0.85 (3H, d, *J* = 7.4 Hz, Me-5), 0.82 (3H, d, *J* = 7.0 Hz, Me-8), 0.59 (6H, q, *J* = 8.0 Hz,

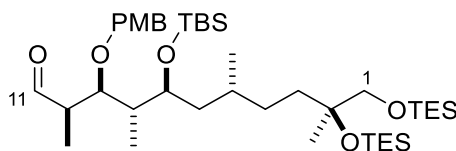
Si(CH₂CH₃)₃), 0.57 (6H, q, J = 7.8 Hz, Si(CH₂CH₃)₃), 0.05 (3H, s, Si(CH₃)₃(CHb₃)), 0.02 (3H, s, Si(CH₃)₃(CHb₃)); ¹³C NMR (125 MHz, CDCl₃): δ_c 158.9, 131.2, 128.6, 113.7, 80.7, 75.9, 73.5, 69.9, 69.6, 66.2, 55.3, 42.6, 38.4, 37.8, 37.1, 31.9, 29.4, 25.9, 25.3, 19.4, 18.1, 15.3, 10.2, 9.9, 7.2, 6.8, 4.4, -4.2, -4.7; HRMS (ES⁺): calc. for C₄₁H₈₀O₆Si₃Na [M+Na]⁺ 777.5317, found 777.5315.

(2*S*,5*R*,7*S*,8*R*,9*R*,10*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-2,5,8,10-tetramethyl-2-((triethylsilyl)oxy)undecane-1,11-diol (199)



R_f 0.12 (3:1 PE/EtOAc); [α]_D²⁰ -25.9 ° (c 0.46, CHCl₃); IR (thin film, ν_{max}/cm⁻¹): 3551, 3443, 1614, 1510, 1462, 1248, 1052, 822, 741; ¹H NMR (500 MHz, CDCl₃): δ_H 7.25 (2H, d, J = 8.7 Hz, H-Ar), 6.87 (2H, d, J = 8.7 Hz, H-Ar), 4.52 (1H, d, J = 11.2 Hz, CHaCHbAr), 4.48 (1H, d, J = 11.2 Hz, CHaHbAr), 4.17 (1H, dt, J = 10.9, 2.2 Hz, H-7), 3.80 (3H, s, ArOCH₃), 3.64-3.60 (2H, m, H-11), 3.41 (1H, dd, J = 9.8, 1.9 Hz, H-9), 3.38 (1H, dd, J = 10.7, 6.9 Hz, H-1a), 3.31 (1H, dd, J = 10.7, 5.6 Hz, H-1b), 2.03-1.97 (2H, m, H-8, O-H), 1.95-1.89 (1H, m, H-10), 1.59 (1H, br s, O-H), 1.54-1.21 (7H, m, H-3, H-4, H-5, H-6), 1.19 (3H, s, Me-2), 0.98-0.95 (9H, m, Si(CH₂CH₃)₃), 0.89-0.81 (18H, m, Me-5, Me-8, Me-10, SiC(CH₃)₃), 0.64-0.58 (6H, m, Si(CH₂CH₃)₃), 0.05 (3H, s, Si(CH₃)₃(CHb₃)), 0.02 (3H, s, Si(CH₃)₃(CHb₃)); ¹³C NMR (125 MHz, CDCl₃): δ_c 158.8, 131.1, 128.4, 113.6, 80.5, 76.2, 73.4, 69.8, 69.4, 66.0, 55.2, 42.5, 38.0, 37.7, 37.3, 29.0, 27.6, 25.8, 22.5, 19.3, 18.0, 10.1, 9.7, 7.0, 4.3, -4.3, -4.7; HRMS (ES⁺): calc. for C₃₅H₆₉O₆Si₂ [M+H]⁺ 641.4633, found 641.4641.

(2*R*,3*S*,4*R*,5*S*,7*R*,10*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4,7,10-tetramethyl-10,11-bis((triethylsilyl)oxy)undecanal (200)

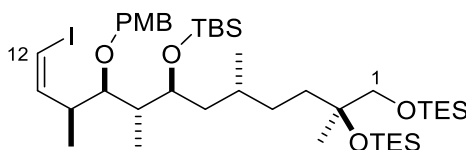


To a solution of alcohol **195** (32 mg, 0.042 mmol, 1.0 equiv.) in CH₂Cl₂ (0.5 mL) were added triacetoxyiodobenzene (36 mg, 0.085, 2.0 equiv.) and NaHCO₃ (10.6 mg, 0.126 mmol, 3.0 equiv.) and stirred for 20 min. Upon completion, Na₂S₂O₃ (0.5 mL) and NaHCO₃ (0.5 mL) were added and stirred

for a further 10 min, before the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 1 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material (31 mg, 97%) was used directly in the following reaction without further purification.

R_f 0.34 (9:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_H 9.83 (1H, s, H-11), 7.17 (2H, d, *J* = 8.7 Hz, H-Ar), 6.83 (2H, d, *J* = 8.7 Hz, H-Ar), 4.28 (1H, d, *J* = 10.8 Hz, CHaHbAr), 4.24 (1H, d, *J* = 10.8 Hz, CHaHbAr), 4.15 (1H, dt, *J* = 9.9, 2.9 Hz, H-7), 3.81 (1H, dt, *J* = 9.4, 2.1 Hz, H-9), 3.79 (3H, ArOCH₃), 3.39 (1H, d, *J* = 9.6 Hz, H-1a), 3.31 (1H, dd, *J* = 9.6, 2.9 Hz, H-1b), 2.52 (1H, q, *J* = 7.1 Hz, H-10), 2.01-1.96 (1H, m, H-8), 1.54-1.23 (7H, m, H-3, H-4, H-5, H-6), 1.17 (3H, d, *J* = 7.1 Hz, Me-10), 1.15 (3H, s, Me-2), 0.95 (9H, t, *J* = 7.9 Hz, Si(CH₂CH₃)₃), 0.93 (9H, t, *J* = 8.1 Hz, Si(CH₂CH₃)₃), 0.87 (9H, s, SiC(CH₃)₃), 0.85 (3H, d, *J* = 7.1 Hz, Me-8), 0.80 (3H, d, *J* = 6.8 Hz, Me-5), 0.59 (6H, q, *J* = 7.9 Hz, Si(CH₂CH₃)₃), 0.56 (6H, q, *J* = 8.1 Hz, Si(CH₂CH₃)₃), 0.02 (3H, s, Si(CH₃)₃(CHb₃)), 0.01 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_C 205.1, 159.1, 130.4, 129.3, 113.6, 79.2, 75.9, 72.6, 69.8, 69.5, 55.2, 55.2, 49.4, 42.2, 38.5, 37.1, 31.8, 29.4, 25.9, 25.3, 25.3, 19.5, 19.4, 18.1, 10.5, 7.2, 6.8, 4.4, -4.2, -4.7.

(5*S*,7*R*,10*S*)-13,13-Diethyl-5-((2*R*,3*R*,4*S*,*Z*)-6-iodo-3-((4-methoxybenzyl)oxy)-4-methylhex-5-en-2-yl)-2,2,3,3,7,10-hexamethyl-10-((triethylsilyl)oxy)-4,12-dioxo-3,13-disilapentadecane (196)



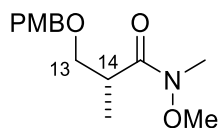
To a stirred suspension of (iodomethyl)triphenylphosphonium iodide (89 mg, 0.170 mmol, 4.0 equiv.) in THF (0.3 mL) at 0 °C was added NaHMDS (1M in THF, 0.14 mL, 0.144 mmol, 3.5 equiv.) and stirred for 30 min. The reaction mixture was then cooled to -78 °C and a solution of aldehyde **200** (31 mg, 0.041 mmol, 1.0 equiv.) in THF (0.3 mL) added *via* cannula, before stirring for a further h. The reaction was then quenched by addition of PE and filtered through a short plug of Celite®, before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give the title compound as a colourless oil (23 mg, 64%).

R_f 0.17 (19:1 PE/EtOAc); $[\alpha]_D^{20} + 14.5^\circ$ (*c* 1.00, CHCl₃); **IR** (thin film, ν_{max}/cm⁻¹): 1514, 1462, 1248, 1065, 836, 771; **¹H NMR** (500 MHz, CDCl₃): δ_H 7.23 (2H, d, *J* = 8.5 Hz, H-Ar), 6.86 (2H, d, *J* = 8.5 Hz, H-Ar), 6.23 (1H, dd, *J* = 8.8, 7.2 Hz, H-11), 6.16 (1H, d, *J* = 7.3 Hz, H-12), 4.47 (1H, d, *J* = 11.0 Hz, CHaHbAr), 4.42 (1H, d, *J* = 11.0 Hz, CHaHbAr), 4.11 (1H, d, *J* = 10.1 Hz, H-7), 3.81 (3H, s, ArOCH₃), 3.40 (1H, d, *J* = 9.4 Hz, H-1a), 3.31 (1H, d, *J* = 9.4 Hz, H-1b), 3.26 (1H, dd, *J* = 9.6, 2.6 Hz, H-9), 2.76-2.70 (1H, m, H-10), 1.99-1.93

(1H, m, H-8), 1.55-1.26 (7H, m, H-3, H-4, H-5, H-6), 1.16 (3H, s, Me-2), 0.96 (9H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.94 (9H, t, $J = 7.9$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.92 (3H, d, $J = 7.2$ Hz, Me-8), 0.82 (3H, d, $J = 6.5$ Hz, Me-5), 0.59 (6H, q, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.57 (6H, q, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.04 (6H, s, $\text{SiC}(\text{CH}_3)_3$), 0.02 (6H, s, $\text{SiC}(\text{CH}_3)_3$); **^{13}C NMR** (125 MHz, CDCl_3): δ_{C} 158.9, 145.5, 131.2, 128.4, 113.6, 83.3, 80.8, 75.9, 74.0, 69.9, 69.5, 55.3, 42.8, 41.8, 38.6, 37.1, 32.0, 29.4, 25.9, 25.3, 22.6, 19.4, 18.1, 12.2, 10.3, 7.2, 6.8, 4.4, -4.1, -4.6; **HRMS** (ES⁺): calc. for $\text{C}_{42}\text{H}_{81}\text{IO}_5\text{Si}_3$ $[\text{M}+\text{H}]^+$ 899.4334, found 899.4336

6.4.2 Preparation of the C₁₃-C₁₉ Vinyl Iodide

(*R*)-*N*-Methoxy-3-((4-methoxybenzyl)oxy)-*N*,2-dimethylpropanamide (**218**)

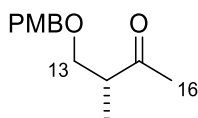


To a slurry of *N*, *O*- dimethylhydroxylamine hydrochloride (16.6 g, 167 mmol, 1.5 equiv.) and methyl ester **223** (26.4 g, 111 mmol, 1.0 equiv.) in THF (150 mL) was added *i*-PrMgCl (3 M in THF, 167 mL, 473 mmol, 4.5 equiv.) over 30 min, maintaining a temperature of –20 °C. The reaction mixture was then left to stir at –10 °C for a further 3 h before quenching with NH₄Cl (200 mL). The layers were separated and the aqueous layer extracted with EtOAc (5 x 80 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (4:1 → 0:1 PE/EtOAc) to give the title compound as an orange liquid (23.7 g, 80%).

R_f 0.18 (3:1 PE/EtOAc); **¹H NMR** (400 MHz, CDCl₃): δ_H 7.23 (2H, d, *J* = 8.6 Hz, H-Ar), 6.86 (2H, d, *J* = 8.6 Hz, H-Ar), 4.48 (1H, d, *J* = 11.7 Hz, OCH₂H_aH_bAr), 4.40 (1H, d, *J* = 11.7 Hz, OCH₂H_aH_bAr), 3.79 (3H, s, ArOMe), 3.69 (1H, app t, *J* = 8.8 Hz, H-13a), 3.68 (3H, s, N(Me)OMe), 3.39 (1H, dd, *J* = 8.8, 5.9 Hz, H-13b), 3.28 - 3.22 (1H, m, H-14), 3.20 (3H, s, N(Me)OMe), 1.10 (3H, d, *J* = 6.8 Hz, Me-14).

Data in agreement with literature values¹⁷⁶

(*R*)-4-((4-Methoxybenzyl)oxy)-3-methylbutan-2-one (**220**)

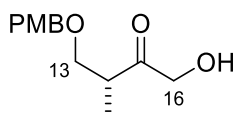


To a solution of Weinreb amide **218** (900 mg, 3.36 mmol, 1.0 equiv.) in THF (24 mL) at 0 °C was added MeMgBr (3 M in Et₂O, 1.68 mL, 5.04 mmol, 1.5 equiv.) dropwise over 10 min and the reaction mixture stirred for 90 min. Upon completion by TLC, the reaction was quenched with NH₄Cl (15 mL) and the layers separated. The aqueous layer was extracted with Et₂O (3 x 10 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 → 7:1 PE/EtOAc) to give the title compound as a pale-yellow oil (669 mg, 81%).

R_f 0.18 (3:1 PE/EtOAc); **¹H NMR** (400 MHz, CDCl₃): δ_H 7.23 (2H, d, *J* = 8.6 Hz, H-Ar), 6.86 (2H, d, *J* = 8.6 Hz, H-Ar), 4.48 (1H, d, *J* = 11.7 Hz, OCH₂H_aH_bAr), 4.40 (1H, d, *J* = 11.7 Hz, OCH₂H_aH_bAr), 3.79 (3H, s, ArOMe), 3.60 (1H, dd, *J* = 9.1, 7.7 Hz, H-13a), 3.43 (1H, dd, *J* = 9.1, 5.5 Hz, H-13b), 2.87 (1H, dqd, *J* = 9.1, 7.0, 5.5 Hz, H-14), 2.17 (3H, s, H-16), 1.07 (3H, d, *J* = 7.0 Hz, Me-14).

Data in agreement with literature values¹⁷⁷

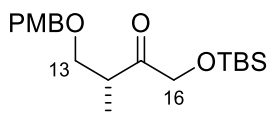
(R)-1-Hydroxy-4-((4-methoxybenzyl)oxy)-3-methylbutan-2-one (222)



To a stirred solution of methyl ketone **220** (1.00 g, 4.08 mmol, 1.0 equiv.) in THF (13 mL) at $-78\text{ }^{\circ}\text{C}$ was added LDA (1 M in THF, 5.70 mL, 5.70 mmol, 1.4 equiv.) *via* cannula. After 1 h at this temperature, TMSCl (0.9 mL, 6.53 mmol, 1.6 equiv.) was added and the solution stirred for another 1 h at this temperature before being allowed to warm to rt over the following h. The reaction mixture was then concentrated *in vacuo* and pentane (10 mL) added. The precipitate formed was filtered through Celite[®] and the filtrate concentrated *in vacuo*. The crude silyl enol ether was then redissolved in *t*-BuOH/H₂O/THF (1:1:1, 20 mL) and OsO₄ (4 wt% in H₂O, 1.4 mL, 0.22 mmol, 0.05 equiv.) and NMO (50 wt% in H₂O, 2.13 mL, 9.10 mmol, 2.2 equiv.) added. The reaction mixture was left to stir for 16 h before being quenched with Na₂S₂O₃ (15 mL) and Et₂O (20 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 20 mL) and EtOAc (20 mL). Combined organic layers were dried over MgSO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (9:1 \rightarrow 4:1 PE/EtOAc) to give the title compound as a colourless oil (880 mg, 82%).

R_f 0.14 (3:1 PE/EtOAc); $[\alpha]_D^{20} - 27.3$ (c 1.15, CHCl₃); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3484, 1717, 1612, 1513, 1456, 1302, 1246, 1094, 1031, 819; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.20 (2H, d, $J = 8.7$ Hz, H-Ar), 6.87 (2H, d, $J = 8.7$ Hz, H-Ar), 4.42 (1H, d, $J = 11.6$ Hz, CHaHbAr), 4.39 (1H, d, $J = 11.6$ Hz, CHaHbAr), 4.35 (1H, dd, $J = 18.6, 4.9$ Hz, H-16a), 4.29 (1H, dd, $J = 18.6, 4.8$ Hz, H-16b), 3.81 (3H, s, ArOCH₃), 3.55 (1H, dd, $J = 8.8, 8.7$ Hz, H-13a), 3.48 (1H, dd, $J = 8.8, 5.1$ Hz, H-13b), 3.13 (1H, dd, $J = 4.9, 4.8$ Hz, O-H), 2.91-2.84 (1H, m, H-14), 1.10 (3H, d, $J = 7.0$ Hz, Me-14); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 212.4, 159.3, 129.7, 129.3, 73.1, 71.7, 68.2, 55.3, 43.0, 13.0; **HRMS** (ES+) calc. for C₁₃H₁₈O₄Na [M+Na]⁺ 261.1103, found 261.1114.

(R)-1-((tert-Butyldimethylsilyl)oxy)-4-((4-methoxybenzyl)oxy)-3-methylbutan-2-one (216)

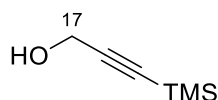


To a solution of alcohol **222** (256 mg, 0.59 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) were added imidazole (60.5 mg, 0.89 mmol, 1.5 equiv.) and TBSCl (107 mg, 0.71 mmol, 1.2 equiv.). The reaction mixture was stirred

for 1 h before being quenched with NH_4Cl (5 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL) and combined organic layers dried over MgSO_4 before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 \rightarrow 5:1 PE/EtOAc) to give the title compound as a colourless oil (310 mg, 85%).

R_f 0.49 (3:1 PE/EtOAc); $[\alpha]_D^{20} - 11.8$ (*c* 1.00, CHCl_3); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2930, 1732, 1613, 1587, 1513, 1463, 1361, 1302, 1246, 1172, 1093, 1033, 939, 836, 779, 668; **¹H NMR** (500 MHz, CDCl_3): δ_{H} 7.21 (2H, d, *J* = 8.3 Hz, H-Ar), 6.86 (2H, d, *J* = 8.3 Hz, H-Ar), 4.43 (1H, d, *J* = 11.5 Hz, CHaHbAr), 4.37 (1H, d, *J* = 11.5 Hz, CHaHbAr), 4.33 (1H, d, *J* = 19.2 Hz, H-16a), 4.26 (1H, d, *J* = 19.2 Hz, H-16b), 3.80 (3H, s, ArOCH_3), 3.58 (1H, t, *J* = 8.5 Hz, H-13a), 3.43 (1H, dd, *J* = 8.5, 5.4 Hz, H-13b), 3.07-2.99 (1H, m, H-14), 1.06 (3H, d, *J* = 7.1 Hz, Me-14), 0.91 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.07 (3H, s, $\text{Si}(\text{CHa}_3)(\text{CHb}_3)$), 0.06 (3H, s, $\text{Si}(\text{CHa}_3)(\text{CHb}_3)$); **¹³C NMR** (125 MHz, CDCl_3): δ_{C} 211.8, 159.2, 130.1, 129.2, 113.7, 72.9, 71.8, 69.5, 55.2, 41.9, 25.6, 18.3, 13.2, -3.6, -5.6; **HRMS** (ES+) calc. for $\text{C}_{19}\text{H}_{32}\text{O}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 375.1968, found 375.2008.

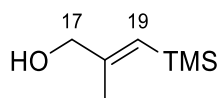
3-(Trimethylsilyl)prop-2-yn-1-ol (224)



A solution of freshly distilled propargyl alcohol (1.00 mL, 17.3 mmol, 1.0 equiv.) in THF (65 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-BuLi (1.6 M, 23.2 mL, 38.0 mmol, 2.2 equiv.) added over 15 min. The reaction mixture was stirred for 40 min. TMSCl (4.80 mL, 38.0 mmol, 2.2 equiv.) was then added dropwise and the solution slowly warmed to rt. After stirring for a further 2 h, the reaction mixture was re-cooled to $0\text{ }^{\circ}\text{C}$ and HCl (1 M, 34.6 mL, 34.6 mmol, 2.0 equiv.) added. After stirring vigorously for 1 h, the layers were separated and the aqueous layer extracted with Et_2O (3 x 30 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless liquid (1.86 g, 84%).

R_f 0.41 (9:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl_3): δ_{H} 4.27 (2H, d, *J* = 6.2 Hz, H-17), 1.56 (1H, t, *J* = 6.2 Hz, O-H), 0.18 (9H, s, $\text{Si}(\text{CH}_3)_3$).

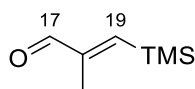
Data in agreement with literature values¹⁷⁸

(E)-2-Methyl-3-(trimethylsilyl)prop-2-en-1-ol (225)

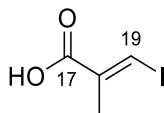
To a stirred suspension of copper (I) iodide (148 mg, 0.78 mmol, 0.2 equiv.) in THF (6 mL) was added a solution of alkyne **224** (500 mg, 3.90 mmol, 1.0 equiv.) in THF (4 mL) and stirred for 5 min. MeMgBr (3 M in Et₂O, 3.25 mL, 9.75 mmol, 2.5 equiv.) was then added dropwise over 5 min and the reaction mixture heated to reflux for 16 h. After cooling to 0 °C, the reaction was quenched with NH₄Cl/NH₄OH (9:1, 10 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 8 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (15:1 PE/EtOAc) gave an inseparable 3:2 mixture of the title compound and starting material.

R_f 0.40 (9:1 PE/EtOAc); **¹H NMR** (400 MHz, CDCl₃): δ_H 5.50 (1H, s, H-19), 4.00 (2H, d, *J* = 4.2 Hz, H-17), 1.76 (3H, s, Me-18), 1.69 (1H, t, *J* = 4.2 Hz, O-H), 0.12 (9H, s, Si(CH₃)₃).

Data in agreement with literature values¹⁷⁹

(E)-2-Methyl-3-(trimethylsilyl)acrylaldehyde (215)

To a solution of allylic alcohol **225** (220 mg, 1.53 mmol, 1.0 equiv.) in Et₂O (8 mL) was added MnO₂ (1.33 g, 15.3 mmol, 10 equiv.) and stirred for 16 h. The reaction mixture was then filtered through Celite®, which was washed with Et₂O (3 mL). The filtrate was concentrated carefully *in vacuo* and then dried over 4Å MS before being used directly in the following reaction, without further purification.

(E)-3-Iodo-2-methylacrylic acid (227)

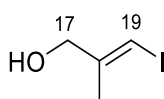
To a suspension of NaH (60% in mineral oil, 2.23 g, 55.5 mmol, 1.2 equiv.) in Et₂O (70 mL) was added diethylmethylmalonate (8.0 mL, 46.4 mmol, 1.0 equiv.) slowly and then heated to reflux for 2 h. Iodoform (18.3 g, 46.4 mmol, 1.0 equiv.) was then added and the reaction mixture refluxed for a further 15 h, before cooling to 0 °C. Et₂O (50 mL) and HCl (3 M, 75 mL) were then added and the solution stirred for 10 min before the layers were separated and the aqueous layer extracted with Et₂O (3 x 40 mL). The product was concentrated *in vacuo* before being redissolved in EtOH (35 mL) and KOH (4 M, 35 mL, 140 mmol, 3.0 equiv.). The solution was then heated to reflux for 16 h before being cooled to rt and

concentrated *in vacuo*. The residue was redissolved in K_2CO_3 (10% *aq*, 100 mL) and the precipitate filtered, washing with CH_2Cl_2 (2 x 30 mL). The filtrate was acidified to pH 1 with conc. HCl and the product extracted with CH_2Cl_2 (8 x 40 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude product was isolated as a yellow-brown solid (6.4 g, 65%) and used without further purification.

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 8.04 (1H, s, H-19), 2.05 (3H, Me-18).

Data in agreement with literature values¹¹²

(*E*)-3-Iodo-2-methylprop-2-en-1-ol (**228**)

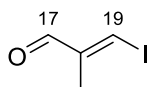


To a solution of carboxylic acid **227** (300 mg, 1.42 mmol, 1.0 equiv.) in Et_2O (6 mL) at 0 °C was added LiAlH_4 (62 mg, 1.62 mmol, 1.15 equiv.) in 4 portions. The reaction mixture was slowly warmed to rt and stirred for 2 h before being quenched with Na_2SO_4 (4 mL) and then H_2SO_4 (1.5 M *aq*, 4 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 8 mL). Combined organic layers were washed with K_2CO_3 (10% *aq*, 10 mL), dried over MgSO_4 , and concentrated *in vacuo*. The crude material was purified by flash column chromatography (4:1 PE/ EtOAc) to give the title compound as a colourless liquid (269 mg, 96%).

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3292, 1619, 1377, 1276, 1068, 1011, 774; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 6.29 (1H, sextet, $J = 1.3$ Hz, H-19), 4.13 (2H, br d, $J = 3.7$ Hz, H-17), 1.85 (3H, d, $J = 1.3$ Hz, Me-18), 1.6 (1H, t, $J = 3.7$ Hz, O-H); **HRMS** (ES+) calc. for $\text{C}_4\text{H}_6\text{IO}$ $[\text{M}-\text{H}]^-$ 196.9458, found 196.9458.

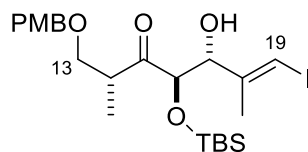
Data in agreement with literature values.¹⁸⁰

(*E*)-3-Iodo-2-methylacrylaldehyde (**214**)



To a solution of allylic alcohol **228** (1.7 g, 8.58 mmol, 1.0 equiv.) in Et_2O (40 mL) was added MnO_2 (7.47 g, 85.8 mmol, 10 equiv.) and stirred for 16 h. The reaction mixture was then filtered through Celite®, which was washed with Et_2O (20 mL). The filtrate was concentrated carefully *in vacuo* and then dried over 4 Å MS before being used directly in the following reaction, without further purification.

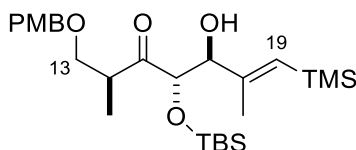
(2*R*,4*R*,5*R*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-7-iodo-1-((4-methoxybenzyl)oxy)-2,6-dimethylhept-6-en-3-one (212)



To a solution of Cy_2BCl (1.01 mL, 5.48 mmol, 1.5 equiv.) in Et_2O (8 mL) at 0 °C was added Et_3N (0.86 mL, 6.21 mmol, 1.7 equiv.) and stirred for 10 min before the addition of a solution of ketone **216** (1.25 g, 3.65 mmol, 1.0 equiv.) in Et_2O (8 mL). The reaction mixture was stirred for a further 75 min before cooling to –78 °C. A solution of aldehyde **214** (2.5 g, 14.6 mmol, 3.5 equiv.) in Et_2O (8 mL) was then added *via* cannula and the reaction mixture allowed to stir at this temperature for 5 h before quenching with MeOH (4 mL), pH 7 buffer (4 mL) and H_2O_2 (30 wt% aq, 2.5 mL) and warming to rt, stirring for a further 30 min. The layers were then separated and the aqueous layer extracted with Et_2O (3 x 8 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/ EtOAc) to give the title compound as a pale-yellow oil (1.61 g, 82%).

R_f 0.26 (9:1 PE/ EtOAc); $[\alpha]_D^{20} + 51.3$ (c 2.49, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3409, 1719, 1613, 1513, 1249, 1075, 838, 778; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.18 (2H, d, $J = 8.7$ Hz, H-Ar), 6.88 (2H, d, $J = 8.7$ Hz, H-Ar), 6.26 (1H, s, H-19), 4.43 (1H, d, $J = 11.7$ Hz, OCHaHbAr), 4.37 (1H, d, $J = 11.7$ Hz, OCHaHbAr), 4.29 (1H, dd, $J = 7.8, 4.9$ Hz, H-17), 3.89 (1H, d, $J = 7.8$ Hz, H-16), 3.81 (3H, s, ArOCH_3), 3.73 (1H, d, $J = 4.9$ Hz, O-H), 3.62 (1H, dd, $J = 10.2, 8.1$ Hz, H-13a), 4.49-4.41 (1H, m, H-14), 3.38 (1H, dd, $J = 8.1, 4.2$ Hz, H-13b), 1.82 (3H, s, Me-18), 1.00 (3H, d, $J = 6.7$ Hz, Me-14), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), –0.02 (3H, s, $\text{Si}(\text{CH}_3)_3$), –0.03 (3H, s, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 213.3, 159.6, 145.3, 129.7, 128.6, 114.0, 81.4, 79.9, 77.1, 73.3, 73.2, 55.3, 40.0, 30.1, 25.7, 23.7, 19.4, 17.9, 14.6, –4.8, –5.1; HRMS (ES+) calc. for $\text{C}_{23}\text{H}_{37}\text{IO}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 571.1353, found 571.1365.

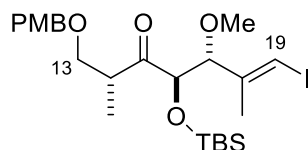
(2*S*,4*S*,5*S*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-1-((4-methoxybenzyl)oxy)-2,6-dimethyl-7-(trimethylsilyl)hept-6-en-3-one (*ent*-213**)**



To a solution of Cy_2BCl (0.13 mL, 0.72 mmol, 1.56 equiv.) in Et_2O (2.5 mL) at 0 °C was added Et_3N (0.11 mL, 0.81 mmol, 1.76 equiv.) and stirred for 10 min before the addition of a solution of ketone **216** (162 mg, 0.46 mmol, 1.0 equiv.) in Et_2O (3 mL). The reaction mixture was stirred for a further 75 min before cooling to –78 °C. A solution of aldehyde **215** (261 mg, 1.84 mmol, 4.0 equiv.) in Et_2O (2.5 mL) was then added *via* cannula and the reaction mixture allowed to stir at this temperature for 5 h. The solution was then warmed to 0 °C and stirred for 90 min before quenching with MeOH (4 mL), pH 7 buffer (4 mL) and H_2O_2 (30 wt% aq, 2.5 mL) and warming to rt, stirring for a further 30 min. The layers were then separated and the aqueous layer extracted with Et_2O (3 x 8 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/ EtOAc) to give the title compound as a pale-yellow oil (183 mg, 81%).

R_f 0.31 (9:1 PE/ EtOAc); $[\alpha]_D^{20} - 12.9$ (c 0.10, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3424, 1718, 1614, 1514, 1463, 1302, 1247, 1173, 1074, 836, 777, 690; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.20 (2H, d, $J = 8.6$ Hz, H-Ar), 6.87 (2H, d, $J = 8.6$ Hz, H-Ar), 5.56 (1H, s, H-19), 4.45 (1H, d, $J = 11.9$ Hz, CHaCHbAr), 4.37 (1H, d, $J = 11.9$ Hz, CHaCHbAr), 4.29 (1H, d, $J = 5.1$ Hz, O-H), 4.18 (1H, dd, $J = 7.2, 5.1$ Hz, H-17), 4.04 (1H, d, $J = 7.2$ Hz, H-16), 3.80 (3H, s, ArOCH_3), 3.59-3.55 (1H, m, H-13a), 3.41-3.33 (2H, m, H-13b, H-14), 1.82 (3H, s, Me-18), 1.00 (3H, d, $J = 6.7$ Hz, Me-14), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.11 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.06 (3H, s, $\text{Si}(\text{CH}_3)_3$), –0.01 (3H, s, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 213.3, 159.4, 151.2, 129.5, 121.0, 127.6, 113.9, 80.8, 79.4, 73.0, 72.9, 55.2, 40.5, 25.7, 18.0, 17.3, 14.4, –0.1, –4.6, –5.1; HRMS (ES+) calc. for $\text{C}_{26}\text{H}_{46}\text{O}_5\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 517.2781, found 517.2786.

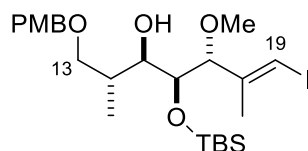
(2*R*,4*R*,5*R*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-7-iodo-5-methoxy-1-((4-methoxybenzyl)oxy)-2,6-dimethylhept-6-en-3-one (210)



To a solution of aldol adduct **212** (1.60 g, 2.97 mmol, 1.0 equiv.) in CH₂Cl₂ (30 mL) was added trimethyloxonium tetrafluoroborate (3.52 g, 23.8 mmol, 8.0 equiv.) and 1,8-Bis(dimethylamino)-naphthalene (6.36 g, 29.7 mmol, 10.0 equiv.) and stirred for 16 h before being quenched with NaHCO₃ (20 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (2 x 10 mL). Combined organic layers were then washed with citric acid (10% aq, 3 x 10 mL) to remove excess 1,8-bis-(dimethylamino)-naphthalene, dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (1.32 g, 82%).

R_f 0.37 (9:1 PE/EtOAc); [α]_D²⁰ + 11.8 (c 0.51, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 2360, 1723, 1613, 1513, 1462, 1248, 1109, 839; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.24 (2H, d, *J* = 8.8 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 6.28 (1H, br s, H-19), 4.43 (1H, d, *J* = 11.8 Hz, OCHaHbAr), 4.39 (1H, d, *J* = 11.8 Hz, OCHaHbAr), 4.11 (1H, d, *J* = 8.0 Hz, H-17), 3.80 (3H, s, ArOCH₃), 3.76 (1H, d, *J* = 8.0 Hz, H-16), 3.54 (1H, dd, *J* = 8.7, 6.8, Hz, H-13a), 3.37-3.29 (2H, m, H-13b, H-14), 3.07 (3H, s, OCH₃), 1.76 (3H, d, *J* = 1.1 Hz, Me-18), 1.06 (3H, d, *J* = 6.5 Hz, Me-14), 0.86 (9H, s, SiC(CH₃)₃), - 0.04 (3H, s, Si(CH₃)₃(CHb₃)), - 0.06 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 212.9, 159.2, 144.6, 130.1, 129.4, 113.8, 87.2, 82.6, 77.8, 72.9, 72.4, 56.4, 55.3, 42.6, 25.7, 18.9, 18.0, 14.1, - 4.8, - 5.1; **HRMS** (ES⁺) calc. for C₂₄H₄₃I O₅NSi [M+NH₄]⁺ 580.1950, found 580.1940.

(2*R*,3*R*,4*S*,5*R*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-7-iodo-5-methoxy-1-((4-methoxybenzyl)oxy)-2,6-dimethylhept-6-en-3-ol (208)

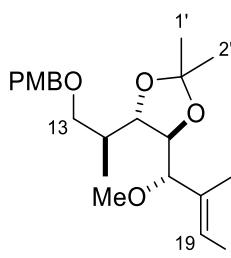


A solution of ketone **210** (930 mg, 1.68 mmol, 1.0 equiv.) in CH₂Cl₂ (20 mL) was cooled to -78 °C and DIBAL (1 M in hexanes, 8.40 mL, 8.42 mmol, 5.0 equiv.) added. The reaction mixture was stirred for 2 h before being quenched with NH₄Cl (10 mL) and NaK tartrate (15 mL) and stirred for a further 2 h.

The layers were then separated and the aqueous layer extracted with CH_2Cl_2 (4 x 20 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a colourless oil (838 mg, 90%).

R_f 0.29 (9:1 PE/EtOAc); $[\alpha]_D^{20} + 2.3$ (c 0.40, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3230, 1613, 1513, 1462, 1248, 1109, 839; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.26 (2H, d, $J = 8.6$ Hz, H-Ar), 6.87 (2H, d, $J = 8.6$ Hz, H-Ar), 6.27 (1H, s, H-19), 4.47 (1H, d, $J = 12.0$ Hz, OCHaHbAr), 4.43 (1H, d, $J = 12.0$ Hz, OCHaHbAr), 3.80 (3H, s, ArOCH_3), 3.81-3.75 (2H, m, H-17, H-13a), 3.68 (1H, dd, $J = 9.0, 4.5$ Hz, H-13b), 3.49 (1H, ddd, $J = 9.2, 8.6, 1.8$ Hz, H-15), 3.40 (1H, dd, $J = 9.2, 6.6$ Hz, H-16), 3.17 (3H, s, OCH_3), 2.76 (1H, d, $J = 8.6$ Hz, O-H), 1.94-1.86 (1H, m, H-14), 1.76 (3H, s, Me-18), 0.97 (3H, d, $J = 6.8$ Hz, Me-14), 0.87 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.07 (3H, s, $\text{Si}(\text{CH}_3)(\text{CHb}_3)$), 0.03 (3H, s, $\text{Si}(\text{CH}_3)(\text{CHb}_3)$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 159.0, 145.2, 130.8, 129.1, 113.7, 86.8, 82.3, 73.8, 73.1, 72.8, 72.1, 56.5, 55.3, 36.2, 26.1, 19.7, 18.3, 14.8, -3.7, -4.1; HRMS (ES+) calc. for $\text{C}_{24}\text{H}_{42}\text{IO}_5\text{Si}$ $[\text{M}+\text{H}]^+$ 565.1841, found 565.1832.

(4*R*,5*S*)-4-((*S*,*E*)-3-Iodo-1-methoxy-2-methylallyl)-5-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolane (242)

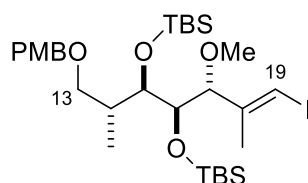


To a solution of silyl ether **208** (10 mg, 0.018 mmol, 1.0 equiv.) in THF (0.5 mL) was added TBAF (1.0 M, 27 μL , 0.027 mmol, 1.5 equiv.) and stirred for 3 h. The reaction was then quenched with NH_4Cl (1 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 x 1 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was redissolved in PE/EtOAc (3:1) and filtered through a short plug of silica, before being used directly in the following reaction.

To a solution of diol **241** (7 mg, 0.016 mmol, 1.0 equiv.) in CH_2Cl_2 (0.4 mL) were added 2,2-methoxypropane (0.3 mL, 2.44 mmol, 150 equiv.) and PPTS (1 crystal). The reaction mixture was stirred for 2 h before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (4:1 PE/EtOAc) to give the title compound as a colourless oil (6.5 mg, 75% over 2 steps).

R_f 0.57 (4:1 PE/EtOAc); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1613, 1513, 1463, 1368, 1247, 1095, 1038, 821; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.26 (2H, d, J = 8.7 Hz, H-Ar), 6.87 (2H, d, J = 8.7 Hz, H-Ar), 6.22 (1H, s, H-19), 4.44 (2H, s, OCH₂Ar), 4.01 (1H, dd, J = 6.8, 6.0 Hz, H-16), 3.88 (1H, app t, J = 6.0 Hz, H-17), 3.81 (3H, s, ArOCH₃), 3.63 (1H, d, J = 6.8 Hz, H-15), 3.61 (1H, dd, J = 9.3, 5.2 Hz, H-13a), 3.36 (1H, dd, J = 9.3, 6.7 Hz, H-13b), 3.19 (3H, s, OCH₃), 2.05 (1H, qdd, J = 7.0, 6.7, 5.2 Hz, H-14), 1.81 (3H, d, J = 1.0 Hz, Me-18), 1.35 (3H, s, H-1'), 1.33 (3H, s, H-2'), 1.00 (3H, d, J = 7.0 Hz, Me-14); **HRMS** (ES+) calc. for C₂₁H₃₅INO₅ [M+NH₄]⁺ 508.1554, found 508.1543.

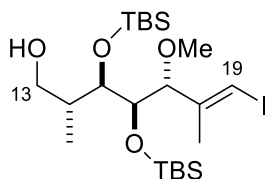
(5*R*,6*R*)-5-((*R,E*)-3-Iodo-1-methoxy-2-methylallyl)-6-((*R*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (252)



To a solution of alcohol **208** (646 mg, 1.17 mmol, 1.0 equiv.) in CH₂Cl₂ (12 mL) at $-78\text{ }^{\circ}\text{C}$ were added TBSOTf (0.32 mL, 1.40 mmol, 1.2 equiv.) and 2,6-lutidine (0.20 mL, 1.75 mmol, 1.5 equiv.) and stirred for 1 h before the addition of NH₄Cl (10 mL). Upon warming to rt, the layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 10 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give the title compound as a pale-yellow oil (746 mg, 96%)

R_f 0.23 (19:1 PE/EtOAc); $[\alpha]_D^{20}$ -9.8 (c 1.90, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1611, 1512, 1462, 1248, 1107, 837, 775; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.26 (2H, d, J = 8.6 Hz, H-Ar), 6.87 (2H, d, J = 8.6 Hz, H-Ar), 6.19 (1H, s, H-19), 4.45 (1H, d, J = 11.9 Hz, OCHaHbAr), 4.39 (1H, d, J = 11.9 Hz, OCHaHbAr), 3.81 (3H, s, ArOCH₃), 3.74 (1H, app t, J = 7.7 Hz, H-17), 3.72 (1H, dd, J = 7.7, 2.3 Hz, H-16), 3.68 (1H, dd, J = 8.1, 2.3 Hz, H-15), 3.56 (1H, dd, J = 9.1, 3.4 Hz, H-13a), 3.24 (1H, dd, J = 9.1, 8.0 Hz, H-13b), 3.07 (3H, s, OCH₃), 2.06 (1H, dqdd, J = 8.0, 6.8, 3.4, 2.3 Hz, H-14), 1.74 (3H, s, Me-18), 1.02 (3H, d, J = 6.8 Hz, Me-14), 0.88 (9H, s, SiC(CH₃)₃), 0.85 (9H, s, SiC(CH₃)₃), 0.07 (3H, s, Si(CHa₃)(CHb₃)), 0.06 (3H, s, Si(CHa₃)(CHb₃)), 0.02 (3H, s, Si(CHa₃)(CHb₃)), 0.00 (3H, s, Si(CHa₃)(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 159.0, 146.4, 131.0, 129.1, 113.7, 85.5, 82.0, 75.2, 73.9, 72.9, 72.6, 55.6, 55.3, 35.8, 26.1, 26.0, 19.4, 18.4, 18.3, 16.1, -3.6 , -3.7 , -4.1 , -4.4 ; **HRMS** (ES+) calc. for C₃₀H₅₆IO₅Si₂ [M+H]⁺ 679.2705, found 679.2698

(2*R*,3*R*,4*R*,5*R*,*E*)-3,4-bis((*tert*-Butyldimethylsilyl)oxy)-7-iodo-5-methoxy-2,6-dimethylhept-6-en-1-ol
(207)



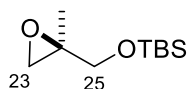
To a solution of PMB ether **252** (720 mg, 1.08 mmol, 1.0 equiv.) in CH₂Cl₂/pH 7 buffer (9:1, 10 mL) at 0 °C was added DDQ (515 mg, 2.27 mmol, 2.1 equiv.) and stirred for 1 h. The reaction was then quenched with NaHCO₃ (10 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 8 mL) and combined organic layers dried over MgSO₄ before being concentrated *in vacuo*.

The crude material was then subjected to Pinnick oxidation conditions to separate the product from the anisaldehyde by-product. The crude mixture was redissolved in *t*-BuOH (5 mL) and a solution of NaClO₂ (360 mg, 4.0 mmol, 3.7 equiv.) and Na₂H₂PO₄ (620 mg, 4.0 mmol, 3.7 equiv.) in H₂O (2 mL) added, followed by 2-methyl-but-2-ene (0.4 mL). The reaction mixture was stirred for 1 h, before being quenched with NaHCO₃ (5 mL) and Et₂O (5 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 5 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 → 4:1 PE/EtOAc) to give the title compound as a colourless oil (542 mg, 90%).

R_f 0.34 (6:1 PE/EtOAc); [α]_D²⁰ + 26.1 (c 0.15, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 3448, 1472, 1361, 1254, 1094, 834, 774; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 6.23 (1H, s, H-19), 3.84 (1H, d, *J* = 8.1 Hz, H-17), 3.73 (1H, dd, *J* = 6.2, 3.1 Hz, H-15), 3.69 (1H, dd, *J* = 8.1, 3.1 Hz, H-16), 3.61 (1H, ddd, *J* = 11.0, 7.1, 3.8 Hz, H-13a), 3.52 (1H, ddd, *J* = 11.0, 8.2, 4.2 Hz, H-13b), 3.10 (3H, s, OCH₃), 2.76 (1H, br s, O-H), 2.14 – 2.06 (1H, m, H-14), 1.74 (3H, s, Me-18), 0.96 (3H, d, *J* = 7.1 Hz, Me-14), 0.92 (9H, s, SiC(CH₃)₃), 0.85 (9H, s, SiC(CH₃)₃), 0.13 (3H, s, Si(CH₃)₃(CHb₃)), 0.11 (3H, s, Si(CH₃)₃(CHb₃)), 0.07 (3H, s, Si(CH₃)₃(CHb₃)), 0.00 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 145.9, 86.2, 82.3, 73.6, 66.6, 60.4, 55.6, 36.0, 26.0, 25.9, 19.4, 18.2, 18.1, 16.7, – 3.5, – 3.9, – 4.5, – 4.6; **HRMS** (ES⁺) calc. for C₂₂H₄₈IO₄Si₂ [M+H]⁺ 559.2130, found 559.2123.

6.4.3 Preparation of the C₂₀-C₂₅ alkene

(*R*)-*tert*-Butyldimethyl((2-methyloxiran-2-yl)methoxy)silane (**258**)

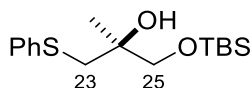


To activated powdered 3 Å MS (1.50 g), were added CH₂Cl₂ (50 mL), L-(+)-diisopropyltartrate (0.13 mL, 0.60 mmol, 0.06 equiv.) and methallyl alcohol (0.84 mL, 10.0 mmol, 1.0 equiv.) at – 20 °C. After stirring for 5 min, Ti(O^{*i*}Pr)₄ (0.15 mL, 0.50 mmol, 0.05 equiv.) was added and the reaction mixture stirred for a further 30 min. Cumene hydroperoxide (80%, 3.60 mL, 20.0 mmol, 2.0 equiv.) was then added and the reaction flask placed in a freezer at – 20 °C for 16 h. The excess peroxide was quenched with the dropwise addition of P(OEt)₃ (2.56 mL, 15.0 mmol, 1.5 equiv.) at –20 °C over 1 h, before Et₃N (2.14 mL, 15.0 mmol, 1.5 equiv.), DMAP (60.5 mg, 0.50 mmol, 0.05 equiv.) and TBSCl (2.26 g, 15.0 mmol, 1.5 equiv.) were added and the reaction stirred for a further h at 0 °C. Upon completion, the reaction mixture was filtered through Celite®. The filtrate was then washed with tartaric acid (10% aq, 20 mL). The layers were separated and the organic layer further washed with NaHCO₃ (2 x 10 mL) and brine (2 x 10 mL), before being dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20:1 PE₃₀₋₄₀ / Et₂O) to give the title compound as a colourless oil (1.42 g, 70%).

R_f 0.25 (9:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_H 3.68 (1H, d, *J* = 11.2 Hz, H-25a), 3.62 (1H, d, *J* = 11.2 Hz, H-25b), 2.77 (1H, d, *J* = 5.0 Hz, H-23a), 2.62 (1H, d, *J* = 5.0 Hz, H-23b), 1.37 (3H, s, Me-24), 0.92 (9H, s, SiC(CH₃)₃), 0.09 (3H, s, Si(CH₃)₃(CHb₃)), 0.08 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_C 66.4, 57.0, 51.4, 25.7, 18.2, 17.9, – 5.5.

Data in agreement with literature values.¹⁶⁴

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-3-(phenylthio)propan-2-ol (**260**)

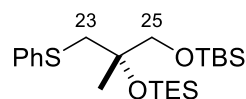


To a stirred solution of epoxide **258** (2.5 g, 12.38 mmol, 1.0 equiv.) in MeOH (70 mL) were added thiophenol (2.52 mL, 24.8 mmol, 2.0 equiv.) and Et₃N (5.17 mL, 37.1 mmol, 3.0 equiv.). The reaction mixture was left to stir for 75 minutes before being quenched with NH₄Cl (50 mL) and the product extracted with CH₂Cl₂ (3 x 40 mL). Combined organic layers were dried over MgSO₄ and the solvent

removed *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to yield the title compound as a colourless oil (3.48 g, 90%)

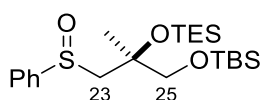
R_f 0.28 (9:1 PE/EtOAc); $[\alpha]_D^{20} - 3.9$ (c 1.00, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 3506, 1472, 1253, 1090, 837, 777, 738, 690; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.37 – 7.09 (5H, m, H-Ar), 3.64 (1H, d, $J = 9.4$ Hz, H-25a), 3.41 (1H, d, $J = 9.4$ Hz, H-25b), 3.17 (1H, d, $J = 12.7$ Hz, H-23a), 3.11 (1H, d, $J = 12.7$ Hz, H-23b), 1.29 (3H, s, Me-24), 0.88 (9H, s, Si(CH₃)₃), 0.04 (3H, Si(CH₃)₃(CHb₃)), 0.03 (3H, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 137.3, 129.3, 128.9, 126.0, 72.9, 68.6, 42.6, 25.9, 23.2, 18.3, – 5.5; **HRMS** (ES+) calc. for C₁₆H₂₈O₂SSiNa [M+Na]⁺ 335.1471, found 335.1470.

(S)-8,8-Diethyl-2,2,3,3,6-pentamethyl-6-((phenylthio)methyl)-4,7-dioxo-3,8-disiladecane (261)



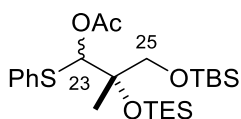
A solution of alcohol **260** (1.08 g, 3.46 mmol, 1.0 equiv.) in CH₂Cl₂ (33 mL) was cooled to – 78 °C and 2,6-lutidine (0.60 mL, 5.19 mmol, 1.5 equiv.) and TESOTf (0.94 mL, 4.15 mmol, 1.2 equiv.) added. The reaction mixture was stirred for 15 min at this temperature, before being stirred for a further h whilst gradually warming to rt. The reaction was then quenched with NH₄Cl (15 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), combined organic layers dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (15:1 PE/EtOAc) to give the title compound as a colourless oil (1.40 g, 96%).

R_f 0.44 (9:1 PE/EtOAc); $[\alpha]_D^{20} + 4.9$ (c 1.00, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1492, 1478, 1100, 1032, 838, 777, 735, 663; **¹H NMR** (400 MHz, CDCl₃): δ_{H} 7.37-7.35 (2H, m, H-Ar), 7.25-7.10 (3H, m, H-Ar), 3.64 (1H, d, $J = 9.5$ Hz, H-25a), 3.41 (1H, d, $J = 9.5$ Hz, H-25b), 3.17 (1H, d, $J = 12.7$ Hz, H-23a), 3.11 (1H, d, $J = 12.7$ Hz, H-23b), 1.29 (3H, s, Me-24), 0.94 (9H, t, $J = 8.0$ Hz, Si(CH₂CH₃)₃), 0.88 (9H, s, Si(CH₃)₃), 0.58 (6H, q, $J = 8.0$ Hz, Si(CH₂CH₃)₃), 0.43 (3H, s, Si(CH₃)₃(CHb₃)), 0.42 (3H, s, Si(CH₃)₃(CHb₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 138.6, 128.7, 128.6, 125.2, 76.2, 69.1, 43.7, 25.9, 18.3, 7.1, 6.7, – 5.4, – 5.5; **HRMS** (ES+) calc. for C₂₂H₄₂O₂SSi₂Na [M+Na]⁺ 449.2336, found 449.2330.

(6R)-8,8-Diethyl-2,2,3,3,6-pentamethyl-6-((phenylsulfinyl)methyl)-4,7-dioxo-3,8-disiladecane (262)

To a stirred solution of sulphide **261** (500 mg, 1.17 mmol, 1.0 equiv.) in CH_2Cl_2 (12 mL) at -5°C was added *meta*-chloroperbenzoic acid (technical grade <77%, 263 mg, 1.17 mmol, 1.0 equiv.) in 5 portions. The reaction mixture was left to stir for 2 h before being quenched with NaHCO_3 (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 6 mL). Combined organic layers were dried over MgSO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3:1 PE/EtOAc) to give the diastereomeric sulfoxides as a colourless oil (451 mg, 88%, 95% brsm).

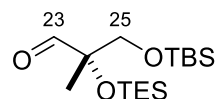
R_f 0.30 (2:1 PE/EtOAc); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1472, 1253, 1190, 1096, 1048, 837, 778, 745; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.64-7.45 (5H, m, H-Ar), 3.81 (0.45H, d, $J = 9.90$ Hz, H-25a), 3.69 (0.45H, d, $J = 9.90$ Hz, H-25b), 3.54 (0.55H, d, $J = 9.7$ Hz, H-25a*), 3.42 (0.55H, d, $J = 9.7$ Hz, H-25b*), 3.05-2.89 (2H, m, H-23), 1.50 (1.65H, s, Me-24*), 1.37 (1.35H, s, Me-24), 1.02-0.94 (9H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.91 (4H, s, $\text{Si}^*(\text{CH}_3)_3$), 0.86 (5H, s, $\text{SiC}(\text{CH}_3)_3$), 0.71-0.59 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.11 (1.3H, m, $\text{Si}^*(\text{CH}_3)_3(\text{CH}_3)_3$), 0.10 (1.3H, m, $\text{Si}^*(\text{CH}_3)_3(\text{CH}_3)_3$), 0.03 (3.4H, $\text{Si}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 146.1, 146.0*, 130.5*, 130.3, 129.1, 129.1*, 123.9, 123.9*, 75.3*, 75.1, 71.0, 70.7*, 69.6*, 69.1, 25.9, 25.9*, 18.3, 18.3*, 7.1, 7.1*, 6.8, 6.7*, -5.3*, -5.4, -5.4*, -5.5; HRMS (ES+) calc. for $\text{C}_{22}\text{H}_{42}\text{O}_3\text{SSi}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 465.291, found 465.2298. * refers to the major diastereomer.

(2R)-3-((tert-Butyldimethylsilyl)oxy)-2-methyl-1-(phenylthio)-2-((triethylsilyl)oxy)propyl acetate (266)

To a stirred solution of sulfoxide **262** (2.67 g, 6.04 mmol, 1.0 equiv.) in acetic anhydride (30 mL) was added NaOAc (2.97 g, 36.2 mmol, 6.0 equiv.) and the reaction mixture heated to reflux for 16 h. After cooling to rt, the solution was diluted with CH_2Cl_2 (100 mL) and NaOH (1 M, aq, 100 mL) added slowly. After stirring for a further 30 min, the layers were separated and the aqueous layer extracted with further CH_2Cl_2 (3 x 50 mL). Combined organic layers were dried over MgSO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (PE \rightarrow 5:1 PE/EtOAc) to give the diastereomeric acetoxysulfides as a colourless oil (2.26 g, 79%).

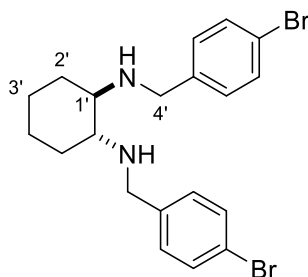
R_f 0.41 (10:1 PE/EtOAc); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1753, 1369, 1222, 1104, 1018, 838, 776, 742 ; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.55-7.50 (2H, m, H-Ar), 7.31-7.22 (3H, m, H-Ar), 6.46 (0.5H, s, H23), 6.29 (0.5H, s, H23*), 3.92 (0.5H, d, J = 9.6 Hz, H-25a), 3.66 (0.5H, d, J = 9.7 Hz, H-25a*), 3.58 (0.5H, d, J = 9.7 Hz, H-25b*), 3.43 (0.5H, d, J = 9.6 Hz, H-25b), 2.05 (1.5H, s, COCH₃*), 2.03 (1.5H, s, COCH₃), 1.39 (1.5H, s, Me-24*), 1.32 (1.5H, s, Me-24), 1.01 (9H, q, J = 8.0 Hz, Si(CH₂CH₃)₃), 0.91 (4.5H, s, Si*(CH₃)₃), 0.90 (4.5H, s, SiC(CH₃)₃), 0.70-0.63 (6H, m, Si(CH₂CH₃)₃), 0.07 (1.5H, s, Si*(CH₃)₂), 0.06 (1.5H, s, Si*(CH₃)₂), 0.05 (3H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 169.7, 169.3*, 134.5, 133.9*, 132.5*, 132.0, 128.8*, 128.7, 127.5*, 127.2, 87.3, 86.3*, 78.6*, 78.4, 68.9, 68.0*, 25.9*, 25.8, 21.1*, 21.0 18.3*, 18.2, 7.1*, 7.0, 6.7, 6.7*, -5.4, -5.4*, -5.5, -5.5*; **HRMS** (ES+) calc. for C₂₄H₄₄O₄SSi₂Na [M+Na]⁺ 507.2397, found 507.2456.

(R)-3-((tert-Butyldimethylsilyl)oxy)-2-methyl-2-((triethylsilyl)oxy)propanal (257)



To a solution of α -acetoxysulphides **266** (2.3 g, 4.85 mmol, 1.0 equiv.) in CH₂Cl₂ (50 mL) at -78 °C was added DIBAL (1 M in hexanes, 7.30 mL, 1.5 equiv.) dropwise and the reaction mixture stirred for 90 min at this temperature. Na₂CO₃ (30 mL) and NaK tartrate (30 mL) were then added and the mixture left to stir for 30 min while warming to rt. The layers were then separated and the aqueous layer extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (19:1 PE/EtOAc) to give the title compound as a colourless oil (1.47 g, 92%).

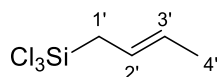
R_f 0.21 (19:1 PE/EtOAc); $[\alpha]_D^{20}$ + 8.1 (c 1.00, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1739, 1463, 1253, 1156, 1107, 1006; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 9.60 (1H, s, H-23), 3.65 (1H, d, J = 10.2 Hz, H-25a), 3.59 (1H, d, J = 10.2 Hz, H-25b), 1.26 (3H, s, Me-24), 0.96 (9H, t, J = 8.0 Hz, Si(CH₂CH₃)₃), 0.87 (9H, s, SiC(CH₃)₃), 0.62 (6H, q, J = 8.0 Hz, Si(CH₂CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 204.3, 80.4, 68.5, 25.8, 20.0, 18.3, 6.9, 6.4, -5.5, -5.6; **HRMS** (ES+) calc. for C₁₆H₃₇O₃Si₂ [M+H]⁺ 333.2276, found 333.2283.

(1*R*,2*R*)-*N*¹,*N*²-bis(4-Bromobenzyl)cyclohexane-1,2-diamine (267)

To a solution of (*R,R*)-1,2-diaminocyclohexane (*L*)-tartrate salt (500 mg, 1.89 mmol, 1.0 equiv.) in H₂O (10 mL), was added K₂CO₃ (522 mg, 3.78 mmol, 2.0 equiv.) then EtOH (5 mL). A solution of methanesulfonic acid (21 mg, 0.22 mmol, 0.12 equiv.) and 4-bromobenzaldehyde (654 mg, 3.78 mmol, 2.0 equiv.) in CH₂Cl₂ (10 mL) was then added and the reaction mixture stirred for 16 h before being heated to reflux for a further h. After cooling to rt, the reaction mixture was concentrated *in vacuo*, H₂O (10 mL) added and the precipitate collected by filtration. The solid was suspended in MeOH (15 mL) and cooled to 0 °C. NaBH₄ (158 mg, 4.26 mmol, 2.26 equiv.) was added and the reaction mixture stirred for 10 min (until gas evolution was complete) and then heated to reflux for 1 h. The reaction mixture was then cooled to rt and concentrated *in vacuo*. To the residue was added NaOH (1 M, 10 mL), EtOAc (10 mL) and PE (10 mL). The layers were separated and the aqueous later extracted with EtOAc/PE (1:1, 2 x 10 mL). Combined organic layers were washed with brine (8 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (4:1 PE/EtOAc) to give the title compound as a pale-yellow amorphous solid (605 mg, 72%).

R_f 0.33 (4:1 PE/EtOAc); **¹H NMR** (500 MHz, CDCl₃): δ_H 7.42 (4H, dt, *J* = 8.3, 1.9 Hz, H-Ar), 7.17 (4H, d, *J* = 8.3 Hz, H-Ar), 3.83 (2H, d, *J* = 13.4 Hz, NCH_aH_bAr x 2), 3.59 (2H, d, *J* = 13.4 Hz, NH_aH_bAr x 2), 2.23-2.11 (4H, m, H-1', H-2'a), 1.79-1.69 (4H, m, NH x 2, H-2'b), 1.23-0.98 (4H, m, H-3').

Data in agreement with literature values.¹²⁹

(*E*)-But-2-en-1-yltrichlorosilane (268)

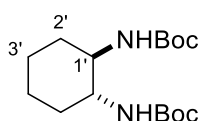
Copper (I) chloride (20.2 mg, 0.20 mmol, 0.02 equiv.) and Et₃N (1.53 mL, 11.0 mmol, 1.1 equiv.) were dissolved in Et₂O (6 mL) and cooled to 0 °C. A solution of *trans*-crotyl bromide (0.98 mL, 10.0 mmol, 1.0 equiv.) and trichlorosilane (1.10 mL, 11.0 mmol, 1.1 equiv.) in Et₂O (3 mL) was then added dropwise over 30 min maintaining the reaction temperature at 0 °C. The resulting solution was stirred for a

further 30 min before warming to rt and stirring for another h. Et₂O and Et₃N were removed by distillation, before the residue was transferred to a separate flask and distilled (bp ~ 140 °C @ 760 mmHg) to give the title compound (968 mg, 51%) as a colourless liquid.

¹H NMR (500 MHz, CDCl₃): δ_H 5.63-5.57 (1H, m, H-2'), 5.41-5.34 (1H, m, H-3'), 2.26 (2H, dt, *J* = 7.6, 1.1 Hz, H-1'), 1.73-1.70 (3H, m, H-4').

Data in agreement with literature values.¹²⁹

Di-*tert*-butyl ((1*R*,2*R*)-cyclohexane-1,2-diyl)dicarbamate (280)

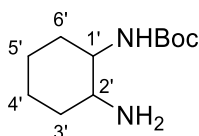


To a solution of (*R,R*)-1,2-diaminocyclohexane (*L*)-tartrate salt (100 mg, 0.38 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) were added di-*tert*-butyl dicarbonate (87 μL, 0.38 mmol, 1.0 equiv.) and Na₂CO₃ (*sat. aq.*, 2.5 mL, 1.9 mmol, 5.0 equiv.). The reaction mixture was stirred for 2 h before being quenched with H₂O (5 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 3 mL), combined organic layers dried over Na₂SO₄ and concentrated *in vacuo* to give the title compound an off-white solid (45 mg, 38%)

¹H NMR (500 MHz, CDCl₃): δ_H 4.89 (2H, br s, N-H), 3.32-3.25 (2H, m, H-1'), 2.04-2.01 (2H, m, H-2'a), 1.73-1.71 (2H, m, H-2'b), 1.43 (18H s, C(CH₃)₃), 1.30-1.14 (4H, m, H-3'); ¹³C NMR (125 MHz, CDCl₃): δ_C 156.5, 79.1, 55.0, 33.0, 28.4, 24.9.

Data in agreement with literature values¹⁸¹

tert-Butyl (2-aminocyclohexyl)carbamate (282)



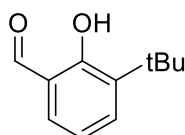
To a stirred solution of conc. HCl (0.35 mL, 4.39 mmol, 1.0 equiv.) in MeOH (1.4 mL) at 0 °C was added racemic diaminocyclohexane (0.53 mL, 4.39 mmol, 1.0 equiv.). The reaction mixture was then warmed to rt and stirred for 15 min before the addition of H₂O (0.4 mL). After a further 30 min, a solution of di-*tert*-butyl dicarbonate (957 mg, 4.39 mmol, 1.0 equiv.) in MeOH (0.5 mL) was added slowly and the

reaction stirred for 16 h. The solution was then concentrated *in vacuo* and the residue treated with 3 M NaOH (3 mL) and extracted with CH₂Cl₂ (3 x 4 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material (680 mg, 72%) was isolated as a beige solid, which was used without further purification.

¹H NMR (500 MHz, CDCl₃): δ_H 4.43 (1H, br s, N-H), 3.16-3.09 (1H, m, H-Cy), 2.31 (1H, td, 10.6, 4.2 Hz, H-Cy), 2.01-1.93 (2H, m, H-Cy), 1.72-1.68 (2H, m, H-Cy), 1.45 (9H, s, CO₂C(CH₃)₃), 1.38 (2H, br s, N-H), 1.28-1.07 (4H, m, H-Cy).

Data in agreement with literature values¹³⁰

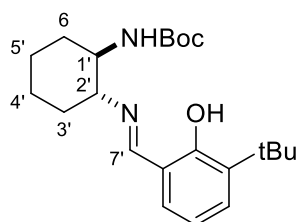
3-(*tert*-Butyl)-2-hydroxybenzaldehyde (284)



To a stirred solution of 2-*tert*-butylphenol (1.53 mL, 10.0 mmol, 1.0 equiv.) in MeCN (20 mL) were added paraformaldehyde (2.02 g, 67.5 mmol, 6.75 equiv.), MgCl₂ (1.43 g, 15.0 mmol, 1.5 equiv.), and Et₃N (5.15 mL, 37.0 mmol, 3.7 equiv.) and heated to reflux for 5 h. After cooling to rt, HCl (5% *aq.*, 10 mL) was added to quench and the mixture was extracted with CH₂Cl₂ (3 x 20 mL). Combined organic layers were concentrated *in vacuo* and the residue partitioned between Et₂O (50 mL) and H₂O (50 mL). The layers were separated and the organic layer washed with brine (15 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was vacuum distilled (bp 72-75 °C @ 5 mm Hg) to give the title compound as a pale-yellow oil (1.10 g, 62%).

¹H NMR (500 MHz, CDCl₃): δ_H 11.81 (1H, s, O-H), 9.88 (1H, s, CHO), 7.53 (1H, d, *J* = 7.6 Hz, H-Ar), 7.42 (1H, d, *J* = 7.6 Hz, H-Ar), 6.96 (1H, t, *J* = 7.6 Hz, H-Ar), 1.42 (9H, s, ArC(CH₃)₃); **HRMS** (ES⁺) calc. for C₁₁H₁₅O₂ [M+H]⁺ 179.1072, found 179.1070.

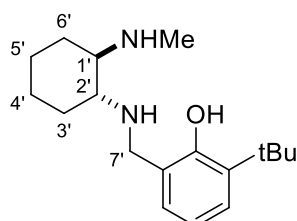
Data in agreement with literature values¹³⁰

tert-Butyl ((1R,2R)-2-(((E)-3-(tert-butyl)-2-hydroxybenzylidene)amino)cyclohexyl)carbamate (278a)

A solution of amine **282** (680 mg, 3.18 mmol, 1.0 equiv.) and aldehyde **284** (566 mg, 3.18 mmol, 1.0 equiv.) in EtOH (30 mL) was heated to reflux and stirred for 3 h. Upon completion, the reaction mixture was cooled to rt and concentrated *in vacuo*. The crude material was purified by recrystallisation from boiling EtOH to give the title compound as yellow crystals (180 mg, 75%)

¹H NMR (500 MHz, CDCl₃): δ_{H} 8.31 (1H, s, H-7'), 7.29 (1H, dd, $J = 7.7, 1.7$ Hz, H-Ar), 7.08 (1H, dd, $J = 7.7, 1.7$ Hz, H-Ar), 6.78 (1H, t, $J = 7.7$ Hz, H-Ar), 4.37 (1H, br s, N-H), 3.62-3.57 (1H, m, H-Cy), 3.01 (1H, br s, H-Cy), 2.11-2.05 (1H, m, H-Cy), 1.98-1.87 (1H, m, H-Cy), 1.92-1.60 (3H, m, H-Cy), 1.49-1.35 (3H, m, H-Cy), 1.48 (9H, s, CO₂C(CH₃)₃), 1.35 (9H, s, ArC(CH₃)₃).

Data in agreement with literature values¹³⁰

2-(tert-Butyl)-6-((((1R,2R)-2-(methylamino)cyclohexyl)amino)methyl)phenol (278b)

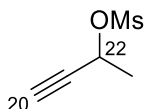
A suspension of LiAlH₄ (54.9 mg, 1.44 mmol, 3.0 equiv.) in THF (3 mL) was cooled to 0 °C and a solution of imine **278a** (180 mg, 0.48 mmol, 1.0 equiv.) in THF (2 mL) added dropwise. The reaction mixture was then heated to reflux for 4 h. After recooling to 0 °C, the reaction was quenched by the dropwise addition of H₂O (5 mL) and the layers separated. The aqueous layer was extracted with Et₂O (3 x 5 mL), combined organic layers dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by recrystallisation from hexanes to give the title compound as white crystals (100 mg, 72%).

¹H NMR (500 MHz, CDCl₃): δ_{H} 7.17 (1H, dd, $J = 7.6, 1.7$ Hz, H-Ar), 6.86 (1H, app d, $J = 7.6$ Hz, H-Ar), 6.70 (1H, t, $J = 7.6$ Hz, H-Ar), 4.01 (1H, d, $J = 13.4$ Hz, H-7'a), 3.83 (1H, d, $J = 13.4$ Hz, H-7'b), 2.39 (3H, s,

NCH_3), 2.21-2.12 (4H, m, H-1', H-2', H-3'a, H-6'a), 1.77-1.69 (2H, m, H-3'b, H-6'b), 1.42 (9H, s, $\text{ArC}(\text{CH}_3)_3$), 1.29-1.14 (3H, m, H-5', H-4'a), 0.99-0.94 (1H, m, H-4'b); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 157.3, 136.7, 126.1, 125.6, 124.3, 118.0, 62.3, 62.1, 50.9, 34.7, 33.4, 31.1, 31.0, 29.5, 25.1, 24.6.

Data in agreement with literature values¹³⁰

But-3-yn-2-yl methanesulfonate (296)

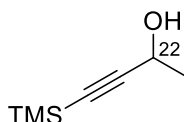


A solution of freshly distilled but-3-yn-2-ol (0.11 mL, 1.43 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL) was cooled to -78°C and Et_3N (0.8 mL, 5.71 mmol, 4.0 equiv.) and MsCl (0.33 mL, 4.28 mmol, 3.0 equiv.) added. The reaction mixture was stirred for 30 min before being quenched with NaHCO_3 (2 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (4:1 PE/ Et_2O) to give the title compound as a colourless liquid (175 mg, 83%).

R_f 0.43 (3:1 PE/ Et_2O); ^1H NMR (500 MHz, CDCl_3): δ_{H} 5.29 (1H, qd, $J = 6.7, 2.1$ Hz, H-22), 3.12 (3H, s, SO_2CH_3), 2.70 (1H, d, $J = 2.1$ Hz, H-20), 1.66 (3H, d, $J = 6.7$ Hz, Me-22).

Data in agreement with literature values¹⁸²

4-(Trimethylsilyl)but-3-yn-2-ol (308)



Procedure A:

To a solution of butyn-1-ol (1.00 mL, 12.7 mmol, 1.0 equiv.) in THF (25 mL) at -78°C was added *n*-BuLi (1.6 M in hexanes, 17.5 mL, 27.9 mmol, 2.2 equiv.) and stirred for 30 min. TMSCl (4.02 mL, 31.8 mmol, 2.5 equiv.) was then added and the reaction mixture stirred for 20 min at this temperature, before being warmed up to rt and stirred for a further 30 min. H_2O (8 mL) and HCl (1 M, aq, 25 mL) were then added and the reaction stirred vigorously for an hour, at which point the layers were separated and the aqueous layer extracted with Et_2O (3 x 20 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 PE/ EtOAc) to give the title compound as a colourless oil (1.53 g, 85%).

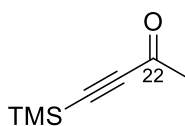
Procedure B:

A solution of ethynyltrimethylsilane (0.1 mL, 0.67 mmol, 1.0 equiv.) in THF (1.2 mL) was cooled to -78°C and *n*-BuLi (1.4 M in hexanes, 0.7 mL, 1.0 mmol, 1.5 equiv.) added dropwise. The reaction mixture was stirred for 30 min before the addition of acetaldehyde (0.19 mL, 3.35 mmol, 5.0 equiv.). The reaction mixture was then slowly warmed to rt over a further 30 min before being quenched with NH_4Cl (1.5 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 x 1 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 PE/EtOAc) to give the title compound as a colourless oil (136 mg, 99%).

R_f 0.27 (9:1 PE/EtOAc); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 4.52 (1H, dq, $J = 6.7, 5.4$ Hz, H-22), 1.80 (1H, d, $J = 5.4$ Hz, O-H), 1.46 (3H, d, $J = 6.7$ Hz, Me-22), 0.18 (9H, s, $\text{Si}(\text{CH}_3)_3$).

Data in agreement with literature values¹⁸³

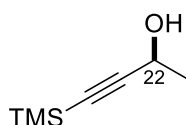
4-(Trimethylsilyl)but-3-yn-2-one (304)



To a solution of oxalyl chloride (1.35 mL, 15.8 mmol, 1.5 equiv.) in CH_2Cl_2 (30 mL) at -78°C was added DMSO (1.49 mL, 21.1 mmol, 2.0 equiv.) and stirred for 15 min. A solution of alcohol **308** (1.5 g, 10.6 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was then added *via* cannula at the reaction mixture stirred for a further 15 min before the dropwise addition of Et_3N (4.41 mL, 31.7 mmol, 3.0 equiv.) The reaction mixture was stirred for 5 min before being slowly warmed to rt over 30 min. NH_4Cl (40 mL) was then added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), combined organic layers dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (1.44 g, 97%).

R_f 0.37 (9:1 PE/EtOAc); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 2.34 (3H, s, Me-22), 0.24 (9H, s, $\text{Si}(\text{CH}_3)_3$).

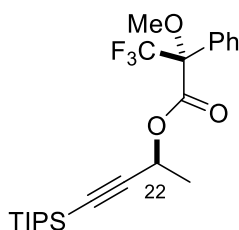
Data in agreement with literature values¹⁸³

(S)-4-(Trimethylsilyl)but-3-yn-2-ol (306)

To a solution of ketone **304** (140 mg, 1.0 mmol, 1.0 equiv.) in IPA (5 mL) was added a solution of Ru[(*R,R*)-*p*-TsNCH(C₆H₅)CH(C₆H₅)NH](η⁶-*p*-cymene) (11.1 mg, 0.05 mmol, 0.05 equiv.) in IPA (3 mL) in 3 portions over 8 h before being stirred for a further 40 h. Further catalyst (5.5 mg, 0.025 mmol, 0.025 equiv.) was added at this point and the reaction mixture stirred for another 24 h. The solution was then diluted with Et₂O (10 mL) and washed with H₂O (3 x 8 mL) to remove IPA. Combined aqueous layers were then back-extracted with CH₂Cl₂ (3 x 5 mL) and combined organic layers dried over MgSO₄ and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (5:1 PE/EtOAc) to give the title compound as a colourless oil (110 mg, 77%). Mosher ester analysis (using ¹⁹F NMR) on the corresponding TIPS alkyne gave an ee of 97.8%)

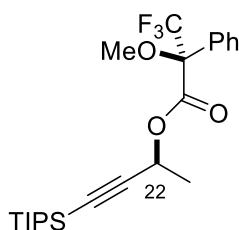
R_f 0.28 (9:1 PE/EtOAc); [α]_D²⁰ = + 22.3 (*c* 0.13, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ_H 4.52 (1H, dq, *J* = 6.7, 5.4 Hz, H-22), 1.80 (1H, d, *J* = 5.4 Hz, O-H), 1.46 (3H, d, *J* = 6.7 Hz, Me-22), 0.18 (9H, s, Si(CH₃)₃).

Data in agreement with literature values¹³⁶

(S)-4-(Triisopropylsilyl)but-3-yn-2-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

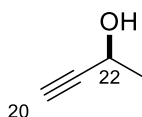
To a solution of alcohol (2.0 mg, 8.0 μmol, 1.0 equiv.) in CH₂Cl₂ (0.2 mL) were added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (10.3 mg, 0.04 mmol, 5.0 equiv.), DCC (9.1 mg, 0.04 mmol, 5.0 equiv.) and DMAP (5.6 mg, 0.04 mmol, 5.0 equiv.). The reaction mixture was stirred for 16 h before being filtered through Celite® and washed with PE (1.0 mL). The filtrate was concentrated *in vacuo* and the residue passed through a short plug of silica to remove excess (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid.

¹H NMR (500 MHz, CDCl₃): δ_H 7.54 (2H, d, *J* = 7.6 Hz, H-Ar), 7.43-7.36 (3H, m, H-Ar), 5.65 (1H, q, *J* = 6.8 Hz, H-22), 3.55 (3H, s, OCH₃), 1.60 (3H, d, *J* = 6.8 Hz, Me-22), 1.03 (18H, app s, Si(CH(CH₃)₂)₃), 0.89-0.86 (3H, m, Si(CH(CH₃)₂)₃); ¹⁹F NMR (500 MHz, CDCl₃): δ_F -71.9.

(S)-4-(Triisopropylsilyl)but-3-yn-2-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

To a solution of propargyl alcohol (2.0 mg, 8.0 μmol , 1.0 equiv.) in CH_2Cl_2 (0.2 mL) were added (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (10.3 mg, 0.04 mmol, 5.0 equiv.), DCC (9.1 mg, 0.04 mmol, 5.0 equiv.) and DMAP (5.6 mg, 0.04 mmol, 5.0 equiv.). The reaction mixture was stirred for 16 h before being filtered through Celite® and washed with PE (1.0 mL). The filtrate was concentrated *in vacuo* and the residue passed through a short plug of silica to remove excess (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid.

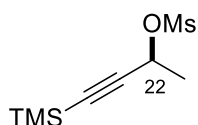
^1H NMR (500 MHz, CDCl_3): δ_{H} 7.56 (2H, d, J = 7.6 Hz, H-Ar), 7.42-7.36 (3H, m, H-Ar), 5.67 (1H, q, J = 6.8 Hz, H-22), 3.59 (3H, s, OCH_3), 1.53 (3H, d, J = 6.8 Hz, Me-22), 1.06 (18H, app s, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 0.92-0.81 (3H, m, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$); **^{19}F NMR** (500 MHz, CDCl_3): δ_{F} -72.2.

(S)-But-3-yn-2-ol (309)

To a solution of silane **306** (50.0 mg, 0.35 mmol, 1.0 equiv.) in THF (3 mL) was added TBAF (1 M, 0.7 mL, 0.7 mmol, 2.0 equiv.) and the reaction mixture stirred for 1 h at rt. The reaction was then quenched with NH_4Cl (1 mL) and Et_2O (1 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 1 mL). Combined organic layers were washed with brine (2 mL), dried over MgSO_4 and carefully concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 $\text{PE}_{30-40}/\text{Et}_2\text{O}$) to give the title compound as a colourless liquid (11.0 mg, 45%).

R_f 0.28 (9:1 PE/EtOAc); **^1H NMR** (500 MHz, CDCl_3): δ_{H} 4.57-4.51 (1H, m, H-22), 2.46 (1H, d, J = 1.9 Hz, H-20), 1.87 (1H, d, J = 5.4 Hz, O-H), 1.48 (3H, d, J = 6.7 Hz, Me-22).

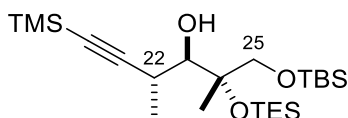
Data in agreement with literature values.¹⁸⁴

(S)-4-(Trimethylsilyl)but-3-yn-2-yl methanesulfonate (317)

To a solution of alcohol **306** (80.0 mg, 0.56 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at -78°C was added Et_3N (0.31 mL, 2.25 mmol, 4.0 equiv.) and MsCl (0.13 mL, 1.69 mmol, 3.0 equiv.) and stirred for 1 h before being quenched with NH_4Cl (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 4 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 \rightarrow 4:1 PE/EtOAc) to give the title compound as a colourless oil (79 mg, 64%).

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 5.25 (1H, q, $J = 6.7$ Hz, H-22), 3.11 (3H, s, SO_2CH_3), 1.62 (3H, d, $J = 6.7$ Hz, Me-22), 0.18 (9H, s, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 101.3, 93.7, 68.6, 39.1, 22.5, -0.5 .

Data in agreement with literature values.¹⁸⁵

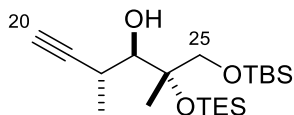
(2S,3R,4R)-1-((tert-Butyldimethylsilyl)oxy)-2,4-dimethyl-2-((triethylsilyl)oxy)-6-(trimethylsilyl)hex-5-yn-3-ol (318)

To a stirred solution of $\text{Pd}(\text{PPh}_3)_4$ (13.9 mg, 0.012 mmol, 0.05 equiv.) in THF (2 mL) at 0°C were added mesylate **317** (85.0 mg, 0.39 mmol, 1.6 equiv.) and aldehyde **258** (80.1 mg, 0.24 mmol, 1.0 equiv.) Et_2Zn (1.1 M in toluene, 0.66 mL, 0.72 mmol, 3.0 equiv.) was then added over 10 min and the reaction mixture stirred for 8 h, before being quenched with NH_4Cl (2 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 2 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a pale-yellow oil (74 mg, 68%).

R_f 0.45 (9:1 PE/EtOAc); $[\alpha]_D^{20} - 11.9$ (c 1.00, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3355, 2240, 1260, 962, 857, 690; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 3.54 (2H, s, H-25), 3.31 (1H, dd, $J = 7.8, 1.6$ Hz, H-23), 3.00 (1H, qd, $J = 7.8, 1.6$ Hz, H-22), 2.69 (1H, d, $J = 7.8$ Hz, O-H), 1.28 (3H, d, $J = 7.8$ Hz, Me-22), 1.28 (3H, s, Me-24), 0.94 (9H, t, $J = 7.9$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.90 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.61 (6H, q, $J = 7.9$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.14 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.07 (6H, s, $\text{Si}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 108.5, 88.2, 77.8, 77.4, 70.5, 28.1,

25.9, 20.9, 20.2, 18.3, 7.1, 6.7, 0.1, – 5.5, –5.6; **HRMS** (ES+) calc. for $C_{23}H_{51}O_3Si_3$ $[M+H]^+$ 459.3141, found 459.3138.

(2*S*,3*R*,4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethyl-2-((triethylsilyl)oxy)-hex-5-yn-3-ol (319)



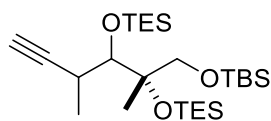
Procedure A:

To a stirred solution of $Pd(PPh_3)_4$ (17.0 mg, 0.015 mmol, 0.05 equiv.) in THF (1 mL) at 0 °C were added a solution of mesylate **296** (80.0 mg, 0.54 mmol, 1.8 equiv.) in THF (2 mL) and a solution of aldehyde **258** (100 mg, 0.30 mmol, 1.0 equiv.) in THF (2 mL). After stirring for 5 min Et_2Zn (15 wt% in toluene, 0.60 mL, 0.66 mmol, 2.2 equiv.) was added dropwise over 20 min. The reaction mixture was then stirred for 16 h at 0 °C and a further 2 h at rt. After re-cooling to 0 °C the NH_4Cl (4 mL) was added to quench and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 3 mL), combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 9:1 PE/ $EtOAc$) to give the title compound as a 1.4:1 mixture of C_{22}/C_{23} *anti* diastereomers (95 mg, 82%).

Procedure B:

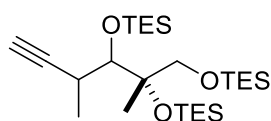
To a solution of silane **318** (50 mg, 0.11 mmol, 1.0 equiv.) in MeOH (1.5 mL) was added K_2CO_3 (76 mg, 0.55 mmol, 5.0 equiv.) and stirred for 90 min. The reaction was quenched with H_2O (2 mL) and extracted with Et_2O (3 x 1 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 10:1 PE/ $EtOAc$) to give the title compound as a colourless oil (33 mg, 78%).

R_f 0.38 (9:1 PE/ $EtOAc$); $[\alpha]_D^{20} + 1.9$ (c 0.32, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3340, 2150, 1260, 981, 832, 765; **1H NMR** (500 MHz, $CDCl_3$): δ_H 3.65 (1H, d, $J = 9.6$ Hz, H-25a), 3.57 (1H, d, $J = 2.0$ Hz, H-23), 3.53 (1H, d, $J = 9.6$ Hz, H-25b), 2.95 (1H, qt, $J = 6.9, 2.2$ Hz, H-22), 2.07 (1H, d, $J = 2.2$ Hz, H-20), 1.31 (3H, d, $J = 6.9$ Hz, Me-22), 1.22 (3H, s, Me-24), 1.02 (9H, t, $J = 7.9$ Hz, $Si(CH_2CH_3)_3$), 0.93 (9H, s, $Si(CH_3)_3$), 0.70 (6H, q, $J = 7.9$ Hz, $Si(CH_2CH_3)_3$), 0.10 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 86.6, 78.0, 74.8, 70.4, 67.8, 27.8, 25.8, 20.5, 20.3, 18.1, 6.9, 5.4, –5.5, –5.6; **HRMS** (ES+) calc. for $C_{20}H_{43}O_3Si_2$ $[M+H]^+$ 387.2745, found 387.2747.

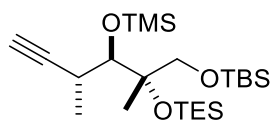
(6S)-7-(But-3-yn-2-yl)-9,9-diethyl-2,2,3,3,6-pentamethyl-6-((triethylsilyl)oxy)-4,8-dioxa-3,9-disilaundecane (320)

To a solution of diastereomeric alcohols **297** (1.9:1 d.r., 10 mg, 0.026 mmol, 1.0 equiv.) in CH_2Cl_2 (0.3 mL) at -78°C were added 2,6-lut. (6 μL , 0.052 mmol, 2.0 equiv.) and TESOTf (9 μL , 0.039 mmol, 1.5 equiv.) sequentially. The reaction mixture was stirred at this temperature for 2 h before being quenched with NH_4Cl (1 mL) and warmed to rt. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 1 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE \rightarrow 15:1 PE/EtOAc) to give the title compound as a mixture of colourless oils with *tris* TES ether **321** (1.9:1 d.r., 10.2 mg, 86%)

R_f 0.35 (15:1 PE/EtOAc); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2124, 1048, 989, 834, 765; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 3.63 (1H, d, $J = 10.2$ Hz, H-25a), 3.38 (1H, d, $J = 10.2$ Hz, H-25b), 3.38 (1H, s, H-23), 3.07 (1H, qt, $J = 7.2, 2.0$ Hz, H-22), 2.00 (1H, d, $J = 2.0$ Hz, H-20), 1.26 (3H, s, Me-24), 1.22 (3H, s, Me-24), 1.01-0.84 (30H, m, Me-22, 2 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$, $\text{SiC}(\text{CH}_3)_3$), 0.69-0.58 (12H, m, 2 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.07 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.06 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$); HRMS (TOF MS) calc. for $\text{C}_{26}\text{H}_{58}\text{O}_3\text{Si}_3$ $[\text{M}+\text{H}]^+$ 501.3615, found 501.3612.

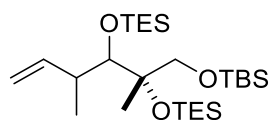
(6S)-5-(But-3-yn-2-yl)-3,3,9,9-tetraethyl-6-methyl-6-((triethylsilyl)oxy)-4,8-dioxa-3,9-disilaundecane (321)

R_f 0.35 (15:1 PE/EtOAc); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2124, 1048, 989, 834, 765; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 3.88 (1H, d, $J = 10.8$ Hz, H-25a), 3.72 (1H, d, $J = 10.8$ Hz, H-25b), 3.34 (1H, s, H-23), 3.17-3.11 (1H, m, H-22), 1.99 (1H, d, $J = 2.4$ Hz, H-20), 1.25 (3H, s, Me-24), 1.01-0.84 (30H, m, Me-22, 3 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.69-0.58 (18H, m, 3 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$); HRMS (TOF MS) calc. for $\text{C}_{26}\text{H}_{58}\text{O}_3\text{Si}_3$ $[\text{M}+\text{H}]^+$ 501.3615, found 501.3612.

(4*R*,5*S*)-4-((*R*)-But-3-yn-2-yl)-2,2,5,8,8,9,9-heptamethyl-5-((triethylsilyl)oxy)-3,7-dioxo-2,8-disiladecane (326)

To a solution of alcohol **323** (26.0 mg, 0.067 mmol, 1.0 equiv.) in CH₂Cl₂ (1.0 equiv.) were added TMSCl (13 μL, 0.10 mmol, 1.5 equiv.) and imidazole (11.3 mg, 0.16 mmol, 2.5 equiv.). The reaction mixture was stirred for 3 h before being quenched with NH₄Cl (1 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 1 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 19:1 PE/EtOAc) to give the title compound as a colourless oil (25 mg, 82%)

R_f 0.28 (19:1 PE/EtOAc); [α]_D²⁰ −6.7 (c 0.75, CHCl₃); **IR** (thin film, ν_{max} /cm^{−1}): 2124, 1048, 989, 834, 765; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 3.66 (1H, d, *J* = 10.2 Hz, H-25a), 3.47 (1H, d, *J* = 10.2 Hz, H-25a), 3.46 (1H, d, *J* = 1.6 Hz, H-23), 2.98 (1H, qdd, *J* = 7.2, 2.5, 1.6 Hz, H-22), 2.03 (1H, d, *J* = 2.5 Hz, H-20), 1.29 (3H, s, Me-24), 1.22 (3H, d, *J* = 7.2 Me-22), 1.01 (9H, t, *J* = 8.0 Hz, Si(CH₂CH₃)₃), 0.93 (9H, s, Si(CH₃)₃), 0.69 (6H, q, *J* = 8.0 Hz, Si(CH₂CH₃)₃), 0.09 (3H, s, Si(CH₃)₃), 0.08 (3H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 109.8, 86.1, 82.6, 79.6, 67.0, 27.9, 26.1, 23.2, 21.7, 18.5, 7.2, 6.6, 0.8, −5.4, −5.4; **HRMS** (ES+) calc. for C₂₃H₅₁O₃Si₃ [M+H]⁺ 459.3141, found 459.3138.

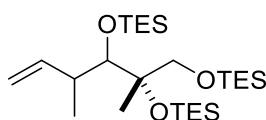
(6*S*)-7-(But-3-en-2-yl)-9,9-diethyl-2,2,3,3,6-pentamethyl-6-((triethylsilyl)oxy)-4,8-dioxo-3,9-disilaundecane (324)

To a solution of alkynes **320** and **321** (41.0 mg, 0.08 mmol, 1.0 equiv.) in MeOH (1 mL) were added Lindlar's catalyst (5% Pd on CaCO₃, 20.0 mg, 0.002 mmol, 0.025 equiv.) and quinoline (18 μL, 0.16 mmol, 2.0 equiv.). After 5 min, the argon line was replaced with an H₂ balloon and the reaction mixture stirred for 16 h. The suspension was then filtered through Celite® and the residue washed with CH₂Cl₂ (2 mL). The filtrate was collected and concentrated *in vacuo*. The crude material was purified by flash column

chromatography (PE → 15:1 PE/EtOAc) to give the title compound as a mixture of colourless oil with *tris* TES ether **325** (31 mg, 75%).

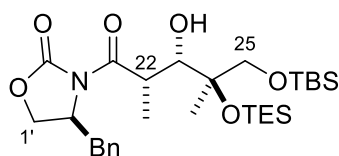
R_f 0.35 (15:1 PE/EtOAc); IR (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1642, 1221, 1084, 953, 771, 687; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_H 6.31-5.94 (1H, m, H-21), 4.96-4.88 (2H, m, H-20), 3.64 (1H, d, $J = 10.2$ Hz, H-25a), 3.61-3.47 (2H, m, H-23, H-25b), 2.81-2.69 (1H, m, H-22), 1.18 (3H, s, Me-24), 1.06 (3H, d, $J = 7.2$ Hz, Me-22), 1.00-0.89 (27H, m, 2 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$, $\text{SiC}(\text{CH}_3)_3$), 0.68-0.57 (12H, m, 2 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.05 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.04 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$); HRMS (TOF MS) calc. for $\text{C}_{26}\text{H}_{58}\text{O}_3\text{Si}_3$ $[\text{M}-\text{H}]^-$ 501.3612, found 501.3612.

(6S)-5-(But-3-en-2-yl)-3,3,9,9-tetraethyl-6-methyl-6-((triethylsilyl)oxy)-4,8-dioxa-3,9-disilaundecane (325)



R_f 0.35 (15:1 PE/EtOAc); IR (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1642, 1221, 1084, 953, 771, 687; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_H 6.31-5.94 (1H, m, H-21), 4.96-4.88 (2H, m, H-20), 3.61-3.47 (2H, m, H-23, H-25a), 3.34 (1H, d, $J = 9.9$ Hz, H-25b), 2.81-2.69 (1H, m, H-22), 1.14 (3H, s, Me-24), 1.07 (3H, d, $J = 7.2$ Hz, Me-22), 1.00-0.89 (27H, m, 3 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.69-0.57 (18H, m, 3 x $\text{Si}(\text{CH}_2\text{CH}_3)_3$); HRMS (TOF MS) calc. for $\text{C}_{26}\text{H}_{58}\text{O}_3\text{Si}_3$ $[\text{M}-\text{H}]^-$ 501.3612, found 501.3612.

(S)-4-(Benzyloxy)-3-((2S,3S,4R)-5-((tert-butyl dimethylsilyl)oxy)-3-hydroxy-2,4-dimethyl-4-((triethylsilyl)oxy)pentanoyl)oxazolidin-2-one (254)

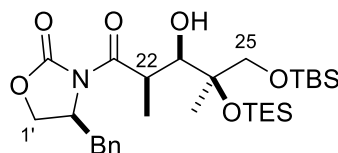


Oxazoline **340** (211 mg, 0.90 mmol, 2.0 equiv.) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. TiCl_4 (105 μL , 0.95 mmol, 2.1 equiv.) was then added and the reaction mixture stirred for 65 mins with additions of DIPEA (173 μL , 1.00 mmol, 2.2 equiv.) and NMP (87 μL , 0.90 mmol, 2.0 equiv.) after 15 mins and 55 mins respectively. At this point, the reaction mixture was cooled to -78 °C and a solution of aldehyde **258** (150 mg, 0.45 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) added *via* cannula. After stirring at this

temperature for a further 2 hours, the reaction mixture was quenched with NH_4Cl (3 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL) and combined organic layers dried over MgSO_4 , with the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (6:1 PE/EtOAc) to give the title compound as a colourless oil (198 mg, 78%, 11:1 d.r.)

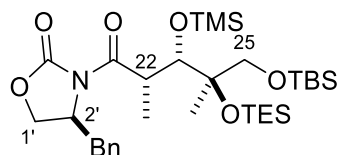
R_f 0.33 (6:1 PE/EtOAc); $[\alpha]_D^{20} = +15.5$ (c 1.00, CHCl_3); IR: (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3500(br), 1783, 1692, 1451, 1208, 1008, 838, 743; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.35-7.21 (5H, m, H-Ar), 4.66 (1H, qd, $J = \text{Hz}$, H-2'), 4.16-4.10 (3H, m, H-1', H-22), 3.95 (1H, dd, $J = 10.0, 5.6$ Hz, H-23), 3.79 (1H, d, $J = 9.7$ Hz, H-25a), 3.34 (1H, d, $J = 9.7$ Hz, H-25b), 3.30 (1H, dd, $J = 13.3, 3.2$ Hz, $\text{CH}_a\text{H}_b\text{Ar}$), 3.02 (1H, d, $J = 10.0$ Hz, O-H), 2.74 (1H, 13.3, 9.8 Hz, $\text{CH}_a\text{H}_b\text{Ar}$), 1.38 (3H, s, Me-24), 1.29 (3H, d, $J = 7.0$ Hz, Me-22), 0.94 (9H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.59 (6H, q, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.08 (3H, s, $\text{Si}(\text{CH}_a\text{CH}_b\text{CH}_3)_3$), 0.07 (3H, s, $\text{Si}(\text{CH}_a\text{CH}_b\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 176.0, 153.1, 135.5, 129.5, 128.9, 127.3, 75.0, 68.9, 65.9, 55.6, 39.2, 37.8, 25.8, 23.2, 18.2, 12.9, 7.0, 6.7, -5.6, -5.6; HRMS (ES+) calc. for $\text{C}_{29}\text{H}_{51}\text{NO}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 588.3153, found 588.3158.

(S)-4-Benzyl-3-((2R,3R,4R)-5-((tert-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethyl-4-((triethylsilyl)oxy)pentanoyl)oxazolidin-2-one (343)



R_f 0.38 (6:1 PE/EtOAc); $[\alpha]_D^{20} = +40.2$ (c 1.00, CHCl_3); IR: (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3500(br), 1783, 1692, 1451, 1208, 1008, 838, 743; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 7.36-7.21 (5H, m, H-Ar), 4.71-4.66 (1H, m, H-2'), 4.32 (1H, d, $J = 9.6$ Hz, O-H), 4.22 (1H, qd, $J = 7.2, 2.5$ Hz, H-22), 4.19-4.14 (2H, m, CH_2Ar), 3.68 (1H, dd, $J = 9.6, 2.4$ Hz, H-23), 3.58 (1H, d, $J = 9.8$ Hz, H-25a), 3.36 (1H, d, $J = 9.8$ Hz, H-25b), 3.23 (1H, dd, $J = 13.5, 2.8$ Hz, H-1'a), 2.73 (1H, dd, $J = 13.5, 9.8$ Hz, H-1'b), 1.40 (3H, d, $J = 7.1$ Hz, Me-22), 1.36 (3H, s, Me-24), 0.92 (9H, t, $J = 7.8$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.88 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.56 (6H, q, $J = 7.8$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.07 (3H, s, $\text{Si}(\text{CH}_a\text{CH}_b\text{CH}_3)_3$), 0.05 (3H, s, $\text{Si}(\text{CH}_a\text{CH}_b\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 178.2, 152.8, 135.2, 129.5, 129.0, 127.4, 79.3, 78.7, 69.1, 65.8, 55.1, 37.7, 34.6, 25.8, 22.2, 18.1, 17.6, 7.0, 6.6, -5.6, -5.7; HRMS (ES+) calc. for $\text{C}_{29}\text{H}_{51}\text{NO}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 588.3153, found 588.3158.

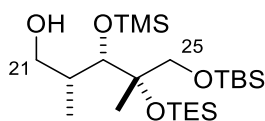
(S)-4-Benzyl-3-((2S,3S,4R)-5-((tert-butyldimethylsilyl)oxy)-2,4-dimethyl-4-((triethylsilyl)oxy)-3-((trimethylsilyl)oxy)pentanoyl)oxazolidin-2-one (354)



A solution of alcohol **254** (217 mg, 0.38 mmol, 1.0 equiv.) in CH₂Cl₂ (4 mL) was cooled to 0 °C and imidazole (47.0 mg, 0.69 mmol, 1.8 equiv.) and TMSCl (65 µL, 0.5 mmol, 1.3 equiv.) added. The reaction mixture was left to stir for 1 h before being quenched with NH₄Cl (3 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 2 mL) and combined organic layers were dried over MgSO₄, before the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (217 mg, 89%).

R_f 0.35 (9:1 PE/EtOAc); $[\alpha]_D^{20} + 9.6$ (c 0.97, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 1788, 1701, 1458, 1387, 1209, 1107, 1009, 838, 741; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.37-7.24 (5H, m, H-Ar), 4.71-4.67 (1H, m, H-2'), 4.24-4.16 (4H, m, H-1', H-22, H-23), 3.69 (1H, d, $J = 10.1$ Hz, H-25a), 3.58 (1H, d, $J = 10.1$ Hz, H-25b), 3.28 (1H, dd, $J = 13.4, 3.2$ Hz, CH₃H_bAr), 2.75 (1H, dd, $J = 13.2, 9.6$ Hz, CH_aH_bAr), 1.22 (3H, s, Me-24), 1.20 (3H, d, $J = 6.8$ Hz, Me-22), 0.94 (9H, t, $J = 8.0$ Hz, Si(CH₂CH₃)₃), 0.94 (9H, s, Si(CH₃)₃), 0.63-0.55 (6H, m, Si(CH₂CH₃)₃), 0.21 (9H, s, Si(CH₃)₃), 0.09 (3H, s, Si(CH₃CH₂CH₃)), 0.08 (3H, s, Si(CH₃CH₂CH₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 176.6, 152.9, 135.8, 129.4, 128.9, 127.2, 79.3, 74.7, 69.1, 65.8, 55.7, 38.4, 38.1, 26.0, 20.8, 18.4, 14.1, 7.1, 6.7, 0.59, -5.3, -5.5; **HRMS** (ES+) calc. for C₃₂H₆₀NO₆Si₃ [M+H]⁺ 638.3723, found 638.3722.

(2R,3S,4R)-5-((tert-butyldimethylsilyl)oxy)-2,4-dimethyl-4-((triethylsilyl)oxy)-3-((trimethylsilyl)oxy)pentan-1-ol (355)

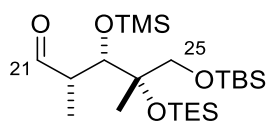


To a stirred solution of amide **354** (210 mg, 0.33 mmol, 1.0 equiv.) in THF (3.5 mL) at 0 °C was added LiBH₄ (4 M in THF, 0.21 mL, 0.83 mmol, 2.5 equiv.) and MeOH (54 µL, 1.23 mmol, 4.0 equiv.) The reaction mixture was stirred for 100 min before being quenched with NH₄Cl (4 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 3 mL). The crude material was purified by column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (129 mg, 85%).

R_f 0.33 (9:1 PE/EtOAc); $[\alpha]_D^{20} + 14.7$ (c 1.00, CHCl₃); **IR** (thin film, $\nu_{\max}/\text{cm}^{-1}$): 3494, 1413, 1251, 1089, 1036, 884, 837, 775, 743, 668; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 3.65 (1H, d, $J = 2.3$ Hz, H-23), 3.61 (1H, d, J

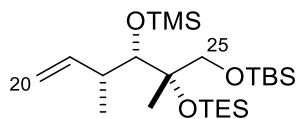
= 10.1 Hz, H-25a), 3.52-3.38 (2H, m, H-21), 3.34 (1H, d, J = 10.1 Hz, H-25b), 2.17-2.09 (1H, m, H-22), 1.81 (1H, t, J = 5.7 Hz, O-H), 1.19 (3H, s, Me-24), 0.94 (9H, t, J = 7.7 Hz, Si(CH₂CH₃)₃), 0.90 (9H, s, Si(CH₃)₃), 0.89 (3H, d, J = 7.1 Hz, Me-22), 0.62 (6H, q, J = 7.7 Hz, Si(CH₂CH₃)₃), 0.11 (9H, s, Si(CH₃)₃), 0.06 (3H, s, Si(CH₃)(CH₂CH₃)), 0.06 (3H, s, Si(CH₃)(CH₂CH₃)); ¹³C NMR (125 MHz, CDCl₃): δ_C 79.7, 77.9, 67.3, 36.8, 25.9, 23.6, 18.4, 12.9, 11.4, 7.0, 6.6, 6.5, 0.60, 0.56, – 5.5, – 5.6; HRMS (ES+) calc. for C₂₂H₅₂O₄Si₃Na [M+Na]⁺ 487.3066, found 487.3059.

(2S,3S,4S)-5-((tert-Butyldimethylsilyl)oxy)-2,4-dimethyl-4-((triethylsilyl)oxy)-3-((trimethylsilyl)oxy)pentanal (356)



To a solution of alcohol **355** (125 mg, 0.27 mmol, 1.0 equiv.) in CH₂Cl₂ (3 mL) was added triacetoxiodobenzene (232 mg, 0.54 mmol, 2.0 equiv.) and anhydrous NaHCO₃ (68.0 mg, 0.81 mmol, 3.0 equiv.) and stirred for 20 min before being quenched with NaHCO₃ (1 mL), and Na₂S₂O₃ (1 mL) and stirred for a further 10 min. The layers were then separated and the aqueous layer extracted with CH₂Cl₂ (3 x 2 mL). Combined organic layers were dried over MgSO₄ and the solvent removed *in vacuo* to give the crude title compound as a colourless oil (120 mg, 96%), which was then used directly in the following reaction without further purification.

R_f 0.28 (15:1 PE/EtOAc); [α]_D²⁰ + 17.3 (c 1.86, CHCl₃); IR (thin film, ν_{max}/cm⁻¹): 1728, 1410, 1280, 838, 780, 667; ¹H NMR (500 MHz, CDCl₃): δ_H 9.56 (1H, d, J = 1.8 Hz, H-21), 3.89 (1H, d, J = 5.7 Hz, H-23), 3.62 (1H, d, J = 10.2 Hz, H-25a), 3.53 (1H, d, J = 10.2 Hz, H-25b), 2.72 (1H, qdd, J = 7.1, 5.7, 1.8 Hz, H-22), 1.19 (3H, s, Me-24), 1.06 (3H, d, J = 7.1 Hz, Me-22), 0.93-0.90 (18H, m, Si(CH₂CH₃)₃, SiC(CH₃)₃), 0.66-0.56 (6H, m, Si(CH₂CH₃)₃), 0.10 (9H, s, Si(CH₃)₃), 0.05 (3H, Si(CH₃)(CH₂CH₃)), 0.05 (3H, Si(CH₃)(CH₂CH₃)); ¹³C NMR (125 MHz, CDCl₃): δ_C 202.9, 78.9, 77.4, 67.0, 48.0, 25.9, 23.5, 18.4, 11.0, 6.9, 6.3, 0.5, – 5.6; HRMS (ES+) calc. for C₂₂H₅₁O₄Si₃ [M+H]⁺ 463.3095, found 463.3087.

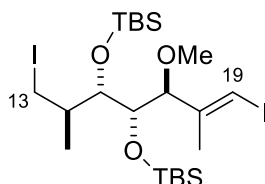
(4S,5S)-4-((R)-But-3-en-2-yl)-2,2,5,8,8,9,9-heptamethyl-5-((triethylsilyl)oxy)-3,7-dioxa-2,8-disiladecane (341)

To a stirred solution of (bromomethyl)triphenylphosphonium bromide (326 mg, 0.91 mmol, 3.5 equiv.) in THF (1.5 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 0.49 mL, 0.78 mmol, 3.0 equiv.) After 20 min, a solution of aldehyde **356** (115 mg, 0.26 mmol, 1.0 equiv.) in THF (1.5 mL) was added and the reaction mixture left to stir for a further hour before being quenched with PE. The precipitate was filtered through Celite® and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (PE → 20:1 PE/EtOAc) to give the title compound as a colourless oil (100 mg, 87%).

R_f 0.36 (20:1 PE/EtOAc); $[\alpha]_D^{20} + 19.7$ (*c* 1.00, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 1461, 1364, 1250, 1216, 1091, 885, 836, 742; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 5.84 (1H, ddd, *J* = 17.3, 10.4, 7.0, H-21), 4.94 (1H, dt, *J* = 17.3, 1.6 Hz, H-20a), 4.92 (1H, ddd, *J* = 10.4, 1.6, 1.3 Hz, H-20b), 3.62 (1H, d, *J* = 9.7 Hz, H-25a), 3.49 (1H, d, *J* = 2.2 Hz, H-23), 3.46 (1H, d, *J* = 9.7 Hz, H-25b), 2.70-2.63 (1H, m, H-22), 1.17 (3H, s, Me-24), 0.96-0.92 (12H, m, Me-22, Si(CH₂CH₃)₃), 0.91 (9H, s, Si(CH₃)₃), 0.64-0.56 (6H, Si(CH₂CH₃)₃), 0.09 (9H, Si(CH₃)₃), 0.05 (3H, Si(CH₃)(CH₃b₃)), 0.05 (3H, Si(CH₃)(CH₃b₃)); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 145.3, 112.3, 81.0, 79.7, 67.6, 37.5, 26.0, 23.7, 18.5, 14.4, 7.1, 6.8, 0.7, -5.4, -5.4; **HRMS** (ES⁺) calc. for C₂₃H₅₂O₃Si₃Na [M+Na]⁺ 483.3116, found 483.3113.

6.4.4 Preparation of Compounds for Model Coupling Studies

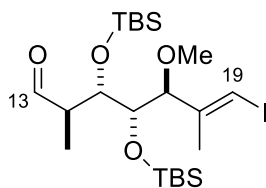
(5*S*,6*S*)-5-((*S*,*E*)-3-iodo-1-methoxy-2-methylallyl)-6-((*R*)-1-iodopropan-2-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (*ent*-359)



PPh₃ (21.7 mg, 0.083 mmol, 1.5 equiv.) and imidazole (5.6 mg, 0.083 mmol, 1.5 equiv.) were dissolved in CH₂Cl₂ (0.5 mL) and stirred for 5 min before the addition of I₂ (21.2 mg, 0.083 mmol, 1.5 equiv.), upon which the solution turned yellow. After a further 5 min, a solution of alcohol **ent-207** (31.0 mg, 0.056 mmol, 1.0 equiv.) in CH₂Cl₂ (0.5 mL) was added and the reaction mixture stirred for 2 h. The reaction was then quenched with NH₄Cl (2 mL) and CH₂Cl₂ (2 mL) and the layers separated. The aqueous layer was extracted with further CH₂Cl₂ (3 x 1 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (15:1 PE/EtOAc) to give the title compound as a colourless oil (32 mg, 87%)

R_f 0.28 (9:1 PE/EtOAc); [α]_D²⁰ + 32.5 (c 0.91, CHCl₃); IR (thin film, ν_{\max} /cm⁻¹): 1472, 1361, 1254, 1094, 834, 774; ¹H NMR (500 MHz, CDCl₃): δ_{H} 6.24 (1H, s, H-19), 3.78-3.74 (2H, m, H-16, H-17), 3.58 (1H, dd, *J* = 8.2, 1.4 Hz, H-15), 3.45 (1H, dd, *J* = 6.8, 2.6 Hz, H-13a), 3.23 (1H, dd, *J* = 9.5, 6.8 Hz, H-13b), 3.12 (3H, s, OCH₃), 1.75 (3H, s, Me-18), 1.72-1.64 (1H, m, H-14), 1.03 (3H, d, *J* = 6.6 Hz, Me-14), 0.91 (9H, s, SiC(CH₃)₃), 0.86 (9H, s, SiC(CH₃)₃), 0.14 (3H, s Si(CH₃)₃(CHb₃)), 0.13 (3H, s, Si(CH₃)₃(CHb₃)), 0.08 (3H, s Si(CH₃)₃(CHb₃)), 0.01 (3H, s, Si(CH₃)₃(CHb₃)); ¹³C NMR (125 MHz, CDCl₃): δ_{C} 146.3, 85.8, 82.4, 74.2, 55.8, 37.1, 26.0, 26.0, 22.6, 19.4, 19.0, 18.4, 18.2, 18.1, -3.6, -3.6, -3.9, -4.3; HRMS (TOF MS) calc. for C₂₂H₄₆I₂O₃Si₂ [M+H]⁺ 669.1153, found 669.1160.

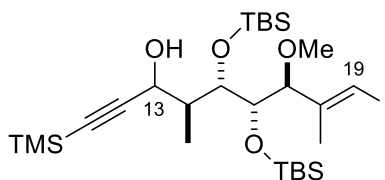
(2R,3S,4S,5S,E)-3,4-bis((tert-Butyldimethylsilyl)oxy)-7-iodo-5-methoxy-2,6-dimethylhept-6-enal
(ent-363)



To a solution of alcohol **ent-207** (40.0 mg, 0.07 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) was cooled to 0 °C and Dess-Martin periodinane (90.8 mg, 0.22 mmol, 3.0 equiv.) and anhydrous NaHCO_3 (36.2 mg, 0.44 mmol, 6.0 equiv.) added. The reaction mixture was warmed to rt and stirred for 30 min before being quenched with NaHCO_3 (1 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (1 mL). After stirring for a further 5 min, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was used without further purification.

R_f 0.48 (6:1 PE/EtOAc); $[\alpha]_D^{20} + 18.4$ (c 1.23, CHCl_3); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1713, 1472, 1361, 1254, 1094, 834, 774; **^1H NMR** (500 MHz, CDCl_3): δ_{H} 9.69 (1H, d, $J = 4.0$ Hz, H-13), 6.24 (1H, s, H-19), 3.89 (1H, dd, $J = 4.2, 2.6$ Hz, H-15), 3.69 (1H, dd, $J = 8.2, 2.6$ Hz, H-16), 3.65 (1H, d, $J = 8.2$ Hz, H-17), 3.01 (3H, s, OCH_3), 2.70 (1H, qdd, $J = 7.2, 4.2, 4.0$ Hz, H-14), 1.73 (3H, s, Me-18), 1.12 (3H, d, $J = 7.2$ Hz, Me-14), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.85 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.11 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.07 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.05 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), -0.01 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$); **^{13}C NMR** (125 MHz, CDCl_3): δ_{C} 205.3, 145.6, 85.9, 82.6, 73.4, 55.2, 46.7, 25.8, 25.8, 22.6, 19.1, 18.2, 18.0, 13.9, -3.7, -4.0, -4.3, -4.7; **HRMS** (ES+) calc. for $\text{C}_{22}\text{H}_{46}\text{IO}_4\text{Si}_2$ $[\text{M}+\text{H}]^+$ 557.1974, found 557.1971

(4S,5S,6S,7S,E)-5,6-bis((tert-Butyldimethylsilyl)oxy)-9-iodo-7-methoxy-4,8-dimethyl-1-(trimethylsilyl)non-8-en-1-yn-3-ol (368)



A solution of ethynyl trimethylsilane (42 μL , 0.30 mmol, 4.2 equiv.) in THF (1 mL) was cooled to -78 °C and *n*-BuLi (1.6 M in hexanes, 0.19 mL, 0.30 mmol, 4.2 equiv.) added. The solution was then stirred for 40 min at this temperature before being warmed to rt for 10 min. Aldehyde **ent-363** (~40 mg, 0.072 mmol, 1.0 equiv.) was dissolved in THF (0.5 mL) and cooled to -78 °C and the lithium acetylide solution added *via* cannula. The reaction mixture was then stirred for 30 min at this temperature and for a further

30 min at rt before being quenched with NH_4Cl (2 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 x 1 mL), combined organic layers dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a 2.5:1 mixture of C_{13} diastereomers (42 mg, 94% over two steps)

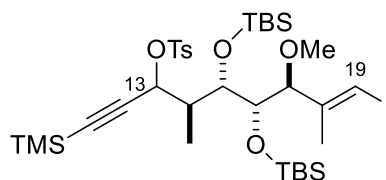
Major diastereomer:

R_f 0.42 (6:1 PE/EtOAc); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3435, 2152, 1472, 1361, 1254, 1094, 834, 774; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 6.26 (1H, s, H-19), 4.52 (1H, dd, $J = 7.3, 2.4$ Hz, H-13), 3.99 (1H, dd, $J = 8.7, 1.9$ Hz, H-17), 3.81-3.77 (2H, m, H-15, H-16), 3.12 (3H, s, OCH_3), 2.18-2.11 (1H, m, H-14), 1.76 (3H, s, Me-18), 1.07 (3H, d, $J = 7.1$ Hz, Me-14), 0.92 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.19 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.18 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.18 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.09 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.02 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 146.0, 106.0, 89.9, 85.8, 82.4, 78.6, 73.9, 69.4, 55.7, 41.2, 26.0, 26.0, 19.6, 18.3, 18.2, 13.4, 0.0, -3.4, -3.5, -4.1, -4.5; HRMS (ES+) calc. for $\text{C}_{27}\text{H}_{56}\text{IO}_4\text{Si}_3$ $[\text{M}+\text{H}]^+$ 655.2526, found 655.2521.

Minor diastereomer

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 6.24 (1H, s, H-19), 4.59 (1H, dd, $J = 6.1, 4.5$ Hz, H-13), 3.85 (1H, d, $J = 7.8$ Hz, H-17), 3.75 (1H, dd, $J = 8.1, 2.7$ Hz, H-15), 3.72 (1H, dd, $J = 7.8, 2.7$ Hz, H-16), 3.10 (3H, s, OCH_3), 2.70 (1H, br s, O-H), 2.18-2.11 (1H, m, H-14), 1.74 (3H, s, Me-18), 1.05 (3H, d, $J = 6.9$ Hz, Me-14), 0.91 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.86 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.17 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.13 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.12 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.09 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$), 0.01 (3H, s, $\text{Si}(\text{CH}_3)_3(\text{CHb}_3)$).

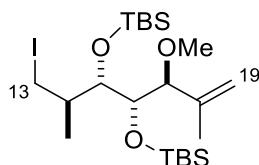
(4*R*,5*S*,6*S*,7*S*,*E*)-5,6-bis((*tert*-Butyldimethylsilyl)oxy)-9-iodo-7-methoxy-4,8-dimethyl-1-(trimethylsilyl)non-8-en-1-yn-3-yl 4-methylbenzenesulfonate (373)



To a solution of diastereomeric alcohols **368** (48.0 mg, 0.073 mmol, 1.0 equiv.) in CH_2Cl_2 /pyridine (1:1, 1.0 mL) was added tosyl chloride (41.6 mg, 0.22 mmol, 3.0 equiv.) and stirred at rt for 2.5 h. The reaction mixture was then quenched with NaHCO_3 (2 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 1 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (12:1 PE/EtOAc) to give an inseparable 2.5:1 ratio of diastereomeric tosylates as a pale-yellow oil (44 mg, 73%).

R_f 0.28 (12:1 PE/EtOAc); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3025, 2152, 1580 1472, 1361, 1254, 1094, 834, 774; **¹H NMR** (major diastereomer, 500 MHz, CDCl₃): δ_{H} 7.93 (2H, d, J = 8.2 Hz, H-Ar), 7.41 (2H, d, J = 8.2 Hz, H-Ar), 6.24 (1H, s, H-19), 4.59 (1H, dd, J = 5.9, 4.3 Hz, H-13), 3.85 (1H, d, J = 7.8 Hz, H-17), 3.81-3.72 (2H, m, H-15, H-16), 3.11 (3H, s, OCH₃), 2.49 (3H, s, ArCH₃), 2.19-2.12 (1H, m, H-14), 1.75 (3H, s, Me-18), 1.05 (3H, d, J = 6.8 Hz, Me-14), 0.91 (9H, s, SiC(CH₃)₃), 0.84 (9H, s, SiC(CH₃)₃), 0.18 (9H, s, Si(CH₃)₃), 0.13 (3H, s, Si(CH₃)₃), 0.13 (3H, s, Si(CH₃)₃), 0.09 (3H, s, Si(CH₃)₃), 0.01 (3H, s, Si(CH₃)₃); **HRMS** (ES⁺) calc. for C₃₄H₆₂IO₆SSi₃ [M+H]⁺ 808.2541, found 808.2547.

(5S,6S)-5-((R)-1-iodopropan-2-yl)-6-((S)-1-methoxy-2-methylallyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (374)



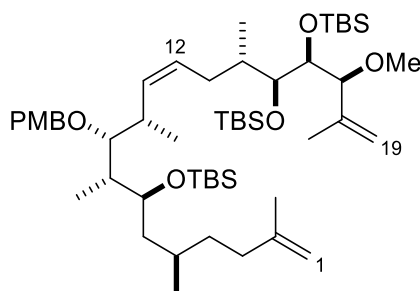
To a solution of vinyl iodide **ent-207** (150 mg, 0.27 mmol, 1.0 equiv.) in THF (2.7 mL) at -78°C was added *n*-BuLi (1.6 M in hexanes, 0.57 mL, 1.08 mmol, 4.0 equiv.) and stirred for 10 min before being warmed up to rt over 1 h. The reaction mixture was then quenched with water (3 mL) and the layers separated. The aqueous layer was extracted with Et₂O (3 x 3 mL) and the combined organic layers dried over MgSO₄ before removal of the solvent *in vacuo*. The crude product was purified by filtration through a short plug of silica gel.

PPh₃ (90.1 mg, 0.34 mmol, 1.5 equiv.) and imidazole (23.1 mg, 0.34 mmol, equiv.) were dissolved in Et₂O/MeCN (1:1, 2 mL), and stirred for 5 min before the addition of I₂ (87.3 mg, 0.34 mmol, 1.5 equiv.). The reaction mixture was then stirred for a further 10 min before a solution of the alcohol (95 mg, 0.23 mmol, 1.0 equiv.) in Et₂O/MeCN (1:1, 1 mL) was added. The suspension was then stirred for a further 1 h before being quenched with NH₄Cl (3 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 3 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (15:1 PE/EtOAc) to give the title compound as a colourless oil (98 mg, 67% over both steps).

R_f 0.36 (9:1 PE/EtOAc); $[\alpha]_{\text{D}}^{20}$ -8.3 (c 0.52, CHCl₃); **IR** (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 1463, 1253, 1101, 874, 834, 774; **¹H NMR** (400 MHz, CDCl₃): δ_{H} 5.05-5.03 (1H, m, H-19a), 4.99-4.98 (1H, m, H-19b), 3.76 (1H, dd, J = 7.2, 2.4 Hz, H-16), 3.63 (1H, d, J = 7.2 Hz, H-17), 3.59 (1H, dd, J = 8.1, 2.4 Hz, H-15), 3.48 (1H, dd, J = 9.3, 2.8 Hz, H-13a), 3.23 (1H, d, J = 9.3, 6.7 Hz, H-13b), 3.14 (3H, s, OCH₃), 1.80-1.71 (1H, m, H-14), 1.68 (3H, s, Me-18), 1.04 (3H, d, J = 6.7 Hz, Me-14), 0.92 (9H, s, SiC(CH₃)₃), 0.86 (9H, s, SiC(CH₃)₃), 0.14 (6H, s,

Si(CH₃)₂), 0.08 (3H, s, Si(CH₃)₂(CHb₃)), 0.04 (3H, s, Si(CH₃)₂(CHb₃)); ¹³C NMR (125 MHz, CDCl₃): δ_c 142.6, 117.3, 85.1, 77.1, 55.3, 37.2, 26.1, 26.0, 19.0, 18.5, 18.3, 17.6, -3.6, -3.7, -4.0, -4.6; HRMS (ES+) calc. for C₂₂H₄₈IO₃Si₂ [M+H]⁺ 543.2187, found 543.2190.

(5S,6R,7R,8S,12S,13S,14S,Z)-13-((tert-Butyldimethylsilyl)oxy)-5-((R)-2,5-dimethylhex-5-en-1-yl)-14-((S)-1-methoxy-2-methylallyl)-7-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,12,16,16,17,17-undecamethyl-4,15-dioxo-3,16-disilaooctadec-9-ene (375)

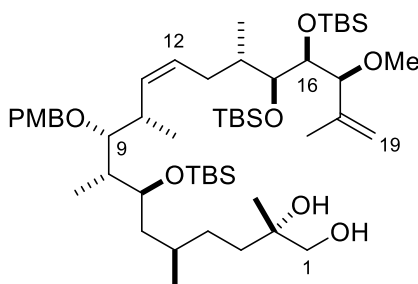


To a solution of iodide **374** (10 mg, 0.018 mmol, 1.0 equiv.) in Et₂O (0.2 mL) at -78 °C was added *t*-BuLi (1.6 M in pentane, 70 μL, 0.11 mmol, 6.0 equiv.) and stirred for 3 min. OMe-9-BBN (1 M in hexanes, 0.18 mL, 0.18 mmol, 10.0 equiv.) was then added, followed by THF (0.2 mL). The reaction mixture was then left to stir for 5 min at this temperature, before being warmed to rt and stirred for a further 1 h. K₃PO₄ (3 M aq, 60 μL, 0.18 mmol, 10.0 equiv.), Pd(dppf)Cl₂ (0.89 mg, 1.35 μmol, 0.075 equiv.) and DMF (0.2 mL) were then added, followed by vinyl iodide **186** (11.5 mg, 0.018 mmol, 1.0 equiv.) The resulting solution was stirred for 16 h before being heated to 50 °C for a further 3 h. The reaction was then quenched with H₂O (0.5 mL). The layers were separated and the aqueous layer extracted with Et₂O (4 x 0.5 mL). Combined organic layers were washed with brine (1 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 20:1 PE/EtOAc) to give the title compound as pale-yellow oil (9.2 mg, 57 %)

R_f 0.26 (19:1 PE/EtOAc); [α]_D²⁰ -14.7 (c 0.45, CHCl₃); IR (thin film, ν_{max}/cm⁻¹): 1469, 1451, 1411, 1391, 1301, 1168, 1008, 978, 877, 731; ¹H NMR (500 MHz, CDCl₃): δ_H 7.25 (2H, d, *J* = 8.6 Hz, H-Ar), 6.86 (2H, d, *J* = 8.6 Hz, H-Ar), 5.54 (1H, t, *J* = 10.4 Hz, H-11), 5.29-5.23 (1H, m, H-12), 5.03-4.96 (2H, m, H-19), 4.67 (1H, s, H-1a), 4.66 (1H, s, H-1b), 4.56 (1H, d, *J* = 10.9 Hz, OCHaHbAr), 4.39 (1H, d, *J* = 10.9 Hz, OCHaCHbAr), 4.15 (1H, dt, *J* = 10.5, 2.4 Hz, H-7), 3.80 (3H, s, ArOCH₃), 3.75 (1H, dd, *J* = 7.6, 2.8 Hz, H-16), 3.63 (1H, d, *J* = 7.2 Hz, H-17), 3.59 (1H, dd, *J* = 9.3, 6.4 Hz, H-15), 3.15 (3H, s, OCH₃), 3.10 (1H, dd, *J* = 10.1, 2.0 Hz, H-9), 2.71-2.65 (1H, m, H-10), 2.41 (1H, dd, *J* = 12.1, 5.7 Hz, H-13a), 2.01 (2H, t, *J* = 8.0 Hz, H-3), 1.93 (1H, qt, *J* = 7.0, 2.8 Hz, H-8), 1.84-1.78 (2H, m, H-14, H-13b), 1.71 (3H, s, Me-2), 1.67 (3H, s, Me-18), 1.41-1.14 (5H, m, H-6, H-5, H-4), 0.97 (3H, d, *J* = 7.1 Hz, Me-10), 0.94-0.85 (33H, m, 3 x Si(CH₃)₃, Me-14, Me-8),

0.80 (3H, d, $J = 6.5$ Hz, Me-5), 0.11-0.01 (18H, m, 3 x Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃): δ_C 158.8, 146.4, 142.6, 135.5, 131.6, 128.4, 128.0, 117.0, 113.6, 109.5, 85.0, 74.0, 69.4, 55.4, 55.3, 43.0, 38.3, 36.6, 35.9, 35.4, 33.9, 31.6, 30.5, 28.6, 26.2, 26.2, 26.0, 26.0, 22.5, 20.6, 19.1, 18.6, 18.5, 18.1, 17.7, 17.2, 13.4, 10.1, -3.6, -3.6, -3.8, -4.1, -4.2, -4.6; HRMS (ES⁺) calc. for C₅₂H₉₉O₆Si₃ [M+H]⁺ 903.6749, found 903.6733.

(2*S*,5*R*,7*S*,8*R*,9*R*,10*S*,14*S*,15*S*,16*S*,17*S*,*Z*)-7,15,16-tris((*tert*-Butyldimethylsilyl)oxy)-17-methoxy-9-((4-methoxybenzyl)oxy)-2,5,8,10,14,18-hexamethylnonadeca-11,18-diene-1,2-diol (376)

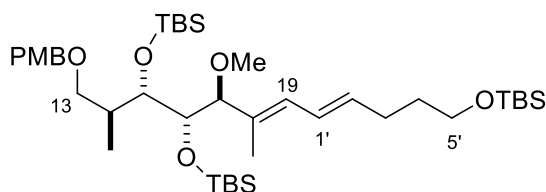


To a solution of alkene **375** (2.0 mg, 2.2 μmol, 1.0 equiv.) in *t*-BuOH/H₂O/THF (1:1:1, 0.1 mL) was added AD_{mix}α (5.1 mg, 0.022 mmol, 10 equiv.) and stirred for 16 h. At this point further K₂OsO₂(OH)₄ (1.6 mg, 4.4 μmol, 2.0 equiv.) and (DHQ)₂PHAL (5.1 mg, 6.6 μmol, 3.0 equiv.) were added and the reaction mixture stirred for a further 4 h. Upon completion, the reaction was diluted with Et₂O (0.3 mL) and quenched with Na₂S₂O₃ (0.2 mL) and NaHCO₃ (0.2 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 x 0.3 mL). Combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (1.2 mg, 58%).

R_f 0.24 (9:1 PE/EtOAc); [α]_D²⁰ -19.2 (c 0.11, CHCl₃); IR (thin film, ν_{max}/cm⁻¹): 3452, 3381, 1469, 1411, 1301, 1168, 1008, 978, 877, 731; ¹H NMR (500 MHz, CDCl₃): δ_H 7.24 (2H, d, $J = 8.6$ Hz, H-Ar), 6.86 (2H, d, $J = 8.6$ Hz, H-Ar), 5.53 (1H, t, $J = 10.6$ Hz, H-11), 5.28-5.23 (1H, m, H-12), 5.02 (1H, s, H-19a), 4.98 (1H, s, H-19b), 4.56 (1H, d, $J = 10.9$ Hz, OCHaHbAr), 4.39 (1H, d, $J = 10.9$ Hz, OCHaHbAr), 4.15 (1H, dt, $J = 10.8, 2.2$ Hz, H-7), 3.80 (3H, s, ArOCH₃), 3.76-3.73 (2H, m, H-1a, H-17), 3.63 (1H, d, $J = 7.7$ Hz, H-1b), 3.58 (1H, dd, $J = 8.0, 1.4$ Hz, H-16), 3.46-3.44 (1H, m, H-15), 3.15 (3H, s, OCH₃), 3.09 (1H, dd, $J = 10.0, 2.4$ Hz, H-9), 2.70-2.64 (1H, m, H-10), 2.40 (1H, ddd, $J = 11.7, 4.4, 1.5$ Hz, H-13a), 1.93 (1H, ddq, $J = 10.8, 10.0, 6.9$ Hz, H-8), 1.86-1.84 (1H, m, H-14), 1.82-1.78 (2H, m, H-13b, O-H), 1.69 (1H, d, $J = 4.3$ Hz, H-6a), 1.67 (3H, s, Me-18), 1.50 (3H, s, Me-2), 1.36-1.22 (6H, m, H-6b, H-5, H-4, H-3), 0.97 (3H, d, $J = 6.8$ Hz, Me-10), 0.93-0.80 (36H, m, 3 x Si(CH₃)₃, Me-14, Me-8, Me-5), 0.11-0.00 (18H, 3 x Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃): δ_C 158.8, 145.7, 142.6, 135.5, 131.5, 128.4, 117.0, 113.6, 84.9, 76.8, 74.1, 69.6, 65.0, 62.1, 58.7, 55.4, 55.3, 53.4, 41.4, 36.4, 36.1, 33.7, 29.7, 29.0, 28.9, 27.7, 26.2, 26.1, 25.8, 22.6, 20.5, 19.4, 18.8, 18.1, 14.3,

11.4, 8.9, -3.6, -3.6, -4.1, -4.2, -4.2, -4.6; **HRMS** (ES+) calc. for C₅₂H₁₀₁O₈Si₃ [M+H]⁺ 937.6804, found 937.6813.

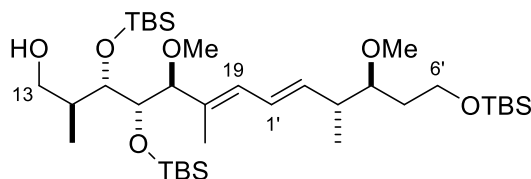
(5*S*,6*S*,7*S*,8*E*,10*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-5-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,3,3,8,16,16,17,17-nonamethyl-4,15-dioxo-3,16-disilaoctadeca-8,10-diene (378)



To a solution of vinyl iodide **ent-252** (50.0 mg, 0.075 mmol, 1.0 equiv.) and alkene **377** (30.5 mg, 0.15 mmol, 2.0 equiv.) in degassed DMF (1 mL) were added Pd(OAc)₂ (1.4 mg, 7.5 μmol, 0.1 equiv.) and Ag₂CO₃ (20.5 mg, 0.075 mmol, 1.0 equiv.). The reaction mixture was heated to 80 °C for 16 h. After recooling to rt, H₂O (2 mL) and Et₂O (2 mL) were added and the layers separated. The aqueous layer was extracted with Et₂O (3 x 2 mL), combined organic layers dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (20:1 PE/EtOAc) to give the title compound as a yellow oil (24 mg, 43%).

R_f 0.31 (20:1 PE/EtOAc); [α]_D²⁰ -5.6 (c 0.70, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 2928, 2340, 1490, 1421, 1249, 1095, 836, 774; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.25 (2H, d, *J* = 8.7 Hz, H-Ar), 6.86 (2H, d, *J* = 8.7 Hz, H-Ar), 6.25 (1H, dd, *J* = 15.2, 10.9, Hz, H-1'), 5.93 (1H, d, *J* = 10.9 Hz, H-19), 5.64 (1H, dt, *J* = 15.2, 7.0 Hz, H-2'), 4.44 (1H, d, *J* = 11.6 Hz, CHaHbAr), 4.39 (1H, d, *J* = 11.6 Hz, CHaHbAr), 3.80 (3H, s, ArOCH₃), 3.72-3.67 (2H, m, H-13), 3.61 (2H, t, *J* = 6.4 Hz, H-5'), 3.61-3.57 (1H, m, H-16), 3.53 (1H, d, *J* = 8.1 Hz, H-17), 3.23 (1H, t, *J* = 8.6 Hz, H-15), 3.06 (3H, s, OCH₃), 2.23-2.13 (2H, m, H-3'), 2.10-2.06 (1H, m, H-14), 1.65-1.59 (2H, m, H-4'), 1.55 (3H, s, Me-18), 1.00 (3H, d, *J* = 6.7 Hz, Me-14), 0.90-0.81 (27H, m, 3 x Si(CH₃)₃), 0.07-0.05 (18H, m, 3 x Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 158.8, 134.1, 130.8, 130.2, 129.17, 129.1, 126.8, 113.6, 86.4, 75.0, 73.8, 72.8, 71.8, 62.8, 55.3, 55.1, 36.0, 29.5, 29.0, 26.1, 26.0, 26.0, 18.0, 15.9, 12.1, 11.6, -3.7, -4.0, -4.2, -4.4, -4.5, -5.2; **HRMS** (ES+) calc. for C₄₁H₇₉O₆Si₃ [M+H]⁺ 751.5179, found 751.5177

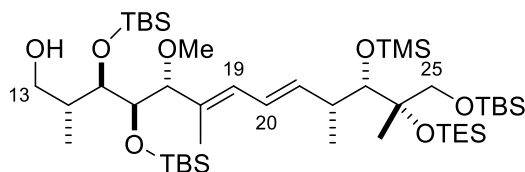
(2*S*,3*S*,4*S*,5*S*,6*E*,8*E*,10*R*,11*S*)-3,4,13-tris((*tert*-Butyldimethylsilyl)oxy)-5,11-dimethoxy-2,6,10-trimethyltrideca-6,8-dien-1-ol (380**)**



Vinyl iodide **ent-207** (40 mg, 0.09 mmol, 1.0 equiv.) and alkene **379** (35.2 mg, 0.14 mmol, 1.5 equiv.) were dissolved in degassed DMF (0.6 mL) and Pd(OAc)₂ (2.0 mg, 9.0 μmol, 0.1 equiv.) and Ag₂CO₃ (24.7 mg, 0.09 mmol, 1.0 equiv.) added. The reaction mixture was then heated to 80 °C and stirred for 16 h. After re-cooling to rt, the reaction was quenched with water (2 mL) and Et₂O (2 mL). The layers were separated and the aqueous layer extracted with further Et₂O (3 x 2 mL). Combined organic layers were washed with brine (2 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give the title compound as a colourless oil (32 mg, 62%)

R_f 0.37 (9:1 PE/EtOAc); [α]_D²⁰ –12.3 (*c* 0.65, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 3628, 1490, 1256, 1098, 836, 757; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 6.24 (1H, dd, *J* = 15.1, 11.0 Hz, H-1'), 5.98 (1H, d, *J* = 11.0 Hz, H-19), 5.60 (1H, dd, *J* = 15.1, 7.8 Hz, H-2'), 3.76 (1H, dd, *J* = 6.1, 2.7 Hz, H-15), 3.68 (2H, t, *J* = 6.3 Hz, H-6'), 3.67 (1H, dd, *J* = 8.1, 2.7 Hz, H-16), 3.63 (1H, d, *J* = 8.1 Hz, H-17), 3.63–3.59 (1H, m, 13a), 3.55 (1H, ddd, *J* = 10.7, 8.5, 4.2 Hz, H-13b), 3.37 (3H, s, OCH₃), 3.25 (1H, dt, *J* = 7.8, 4.4 Hz, H-4'), 3.08 (3H, s, OCH₃), 2.94–2.85 (1H, m, O-H), 2.54 (1H, quint d, *J* = 7.8, 7.0 Hz, H-3'), 2.14–2.08 (1H, m, H-14), 1.66 (3H, s, Me-18), 1.59 (2H, dt, *J* = 6.3, 4.4 Hz, H-5'), 1.02 (3H, d, *J* = 7.0 Hz, Me-14), 0.95 (3H, d, *J* = 7.0 Hz, Me-3'), 0.93 (9H, s, SiC(CH₃)₃), 0.89 (9H, s, SiC(CH₃)₃), 0.81 (9H, s, SiC(CH₃)₃), 0.13–0.06 (18H, m, 3 x Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 136.7, 132.8, 131.1, 126.0, 87.2, 81.5, 73.5, 66.7, 66.6, 59.9, 57.9, 55.1, 39.5, 34.0, 26.0, 25.9, 18.3, 18.2, 18.2, 16.7, 15.2, 12.0, 11.6, 10.6, –3.5, –3.8, –4.6, –4.6, –5.3, –5.3; **HRMS** (ES⁺) calc. for C₃₆H₈₀NO₆Si₃ [M+NH₄]⁺ 706.5288, found 706.5281.

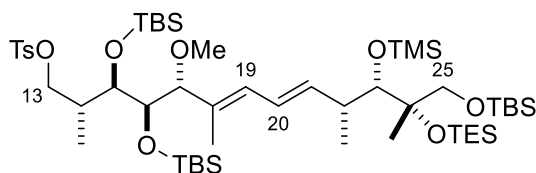
(2*R*,3*R*,4*R*,5*R*,6*E*,8*E*,10*R*,11*S*,12*S*)-3,4,13-tris((*tert*-Butyldimethylsilyl)oxy)-5-methoxy-2,6,10,12-tetramethyl-12-((triethylsilyl)oxy)-11-((trimethylsilyl)oxy)trideca-6,8-dien-1-ol (369)



To a solution of alkene **341** (55 mg, 0.12 mmol, 1.0 equiv.) and vinyl iodide **207** (100.5 mg, 0.18 mmol, 1.5 equiv.) in DMF (1.0 mL) were added Pd(OAc)₂ (5.38 mg, 0.024 mmol, 0.2 equiv.) and Ag₂CO₃ (48.4 mg, 0.144 mmol, 1.2 equiv.). The reaction mixture was heated to 80 °C and stirred for 16 h. After cooling to rt, Et₂O (4 mL) was added and the suspension filtered through a plug of Celite®, washing with further Et₂O. The filtrate was then washed with brine (2 x 3 mL) and dried over MgSO₄, before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 12:1 PE/EtOAc) to give the title compound as a colourless oil (65.9 mg, 65%).

R_f 0.42 (9:1 PE/EtOAc); [α]_D²⁰ + 16.3 (c 0.84, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 3471, 1470, 1463, 1361, 1251, 1091, 834, 774; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 6.18 (1H, dd, *J* = 15.0, 10.9 Hz, H-20), 5.97 (1H, d, *J* = 10.9 Hz, H-19), 5.68 (1H, dd, *J* = 15.0, 7.9 Hz, H-21), 3.76 (1H, dd, *J* = 6.2, 2.8 Hz, H-15), 3.70 (1H, dd, *J* = 8.1, 2.8 Hz, H-16), 3.65-3.59 (2H, m, H-13a, H-17), 3.63 (1H, d, *J* = 9.6 Hz, H-25a), 3.55 (1H, dd, *J* = 8.4, 4.0 Hz, H-13b), 3.49 (1H, d, *J* = 1.7 Hz, H-23), 3.43 (1H, d, *J* = 9.6 Hz, H-25b), 3.08 (3H, s, OCH₃), 2.88 (1H, br s, O-H), 2.77 (1H, dqd, *J* = 7.9, 6.8, 1.7 Hz, H-22), 2.17-2.10 (1H, m, H-14), 1.65 (3H, s, Me-18), 1.16 (3H, s, Me-24), 0.98 (3H, d, *J* = 6.8 Hz, Me-22), 0.97-0.82 (39H, m, Me-14, 3 x SiC(CH₃)₃, Si(CH₂CH₃)₃), 0.62-0.57 (6H, m, Si(CH₂CH₃)₃), 0.14- -0.05 (27H, 3 x Si(CH₃)₂, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 141.4 (C-21), 132.2 (C-18), 131.4 (C-19), 123.9 (C-20), 87.3, 80.7, 79.6, 78.8, 73.4, 67.6, 66.6, 54.9, 36.8, 25.9, 25.8, 25.8, 25.7, 25.6, 23.7, 18.1, 18.0, 14.8, 11.7, 7.1, 6.7, 0.6, -3.7, -4.0, -4.7, -4.7, -5.4, -5.5; **HRMS** (ES⁺) calc. for C₄₈H₁₀₈NO₇Si₅ [M+NH₄]⁺ 950.6966, found 950.6967.

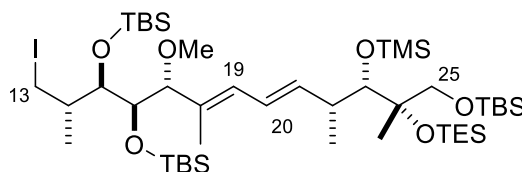
(2R,3R,4R,5R,6E,8E,10R,11R,12S)-3,4,13-tris((tert-Butyldimethylsilyl)oxy)-5-methoxy-2,6,10,12-tetramethyl-12-((triethylsilyl)oxy)-11-((trimethylsilyl)oxy)trideca-6,8-dien-1-yl 4-methylbenzenesulfonate (381)



To a stirred solution of alcohol **369** (25.0 mg, 0.029 mmol, 1.0 equiv.) in CH₂Cl₂/Py (1:1, 0.5 mL) was added tosyl chloride (16.9 mg, 0.089 mmol, 3.0 equiv.). After 4 h the reaction was quenched with NaHCO₃ (1 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 1 mL), combined organic layers dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give the title compound as a colourless oil (22 mg, 75%).

R_f 0.36 (19:1 PE/EtOAc); [α]_D²⁰ + 19.2 (c 0.54, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 2927, 2339, 2012, 1470, 1463, 1361, 1251, 1091, 834, 774; **¹H NMR** (500 MHz, CDCl₃): δ_{H} 7.78 (2H, d, *J* = 8.2 Hz, H-Ar), 7.32 (2H, d, *J* = 8.2 Hz, H-Ar), 6.16 (1H, dd, *J* = 15.0, 10.3 Hz, H-20), 5.91 (1H, d, *J* = 10.3 Hz, H-19), 5.68 (1H, dd, *J* = 15.0, 7.8 Hz, H-21), 4.18 (1H, dd, *J* = 9.5, 3.3 Hz, H-13a), 3.85 (1H, t, *J* = 9.3 Hz, H-13b), 3.66-3.62 (3H, m, H-15, H-17, H-25a), 3.49 (1H, d, *J* = Hz, H-23), 3.47 (1H, d, *J* = 8.4 Hz, H-16), 3.42 (1H, d, *J* = 9.7 Hz, H-25b), 3.01 (3H, s, OCH₃), 2.78-2.72 (1H, m, H-22), 2.44 (3H, s, ArCH₃), 2.19-2.10 (1H, m, H-14), 1.61 (3H, s, Me-18), 1.54 (3H, s, Me-24), 0.99-0.78 (42H, m, Me-14, Me-22, 3 x Si(CH₃)₃), Si(CH₂CH₃)₃), 0.62-0.57 (6H, m, Si(CH₂CH₃)₃), 0.08-0.09 (27H, 3 x Si(CH₃)₂, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃): δ_{C} 144.5 (C-Ar), 142.2 (C-Ar), 141.6 (C-21), 133.2 (C-18), 132.4 (C-Ar), 131.6 (C-19), 129.7 (C-Ar), 124.0 (C-20), 86.6, 80.8, 79.6, 74.2, 74.1, 67.7, 62.4, 54.9, 37.0, 35.2, 29.7, 26.0, 25.9, 25.9, 23.7, 18.5, 18.3, 18.2, 14.9, 14.1, 11.7, 7.1, 6.8, 0.7, -3.7, -3.9, -4.2, -4.6, -5.3, -5.4; **HRMS** (ES⁺) calc. for C₅₂H₁₀₈NO₉SSi₅ [M+NH₄]⁺ 1062.6586, found 1062.6587.

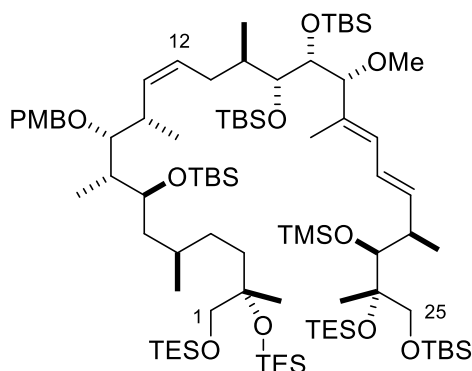
(5*R*,6*R*,7*R*,8*E*,10*E*,12*R*,13*S*,14*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-5-((*S*)-1-iodopropan-2-yl)-7-methoxy-2,2,3,3,8,12,14,17,17,18,18-undecamethyl-14-((triethylsilyl)oxy)-13-((trimethylsilyl)oxy)-4,16-dioxas-3,17-disilanonadeca-8,10-diene (370)



To a stirred solution of tosylate **381** (6.0 mg, 5.7 μmol , 1.0 equiv.) in MeCN (0.15 mL) was added LiI (9.2 mg, 69 μmol , 12 equiv.) and heated to 60 °C. After 3 h a further 12 equivalents of LiI was added and the temperature raised to 70 °C before stirring for a further 2.5 h. Upon completion, the reaction mixture was cooled to rt and quenched with NaHCO_3 (1 mL) and diluted with Et_2O (1 mL). The layers were separated and the aqueous layer extracted with Et_2O (5 x 1.5 mL) before combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE) to give the title compound as colourless oil (4.8 mg, 84%).

R_f 0.35 (19:1 PE/ EtOAc); $[\alpha]_D^{20} + 8.9$ (c 1.00, CHCl_3); IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2956, 2369, 2162, 1420, 1251, 1102, 836, 774; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 6.18 (1H, dd, $J = 15.1, 10.8$ Hz, H-20), 5.95 (1H, d, $J = 10.8$ Hz, H-19), 5.68 (1H, dd, $J = 15.1, 7.9$ Hz, H-21), 3.77 (1H, dd, $J = 7.5, 2.1$ Hz, H-13a), 3.63 (1H, d, $J = 9.6$ Hz, H-25a), 3.61-3.57 (2H, m, H-13b, H-17), 3.49 (1H, d, $J = 2.2$ Hz, H-23), 3.47 (1H, dd, $J = 9.2, 2.7$ Hz, H-16), 3.42 (1H, d, $J = 9.6$ Hz, H-25b), 3.24 (1H, dd, $J = 9.2, 6.6$ Hz, H-15), 3.09 (3H, s, OCH_3), 2.75 (1H, app quint, $J = 7.9$ Hz, H-22), 1.74-1.70 (1H, m, H-14), 1.66 (3H, s, Me-18), 1.54 (3H, s, Me-24), 1.03-0.83 (42H, m, Me-14, Me-22, 3 x $\text{Si}(\text{CH}_3)_3$, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.62-0.57 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.14- -0.03 (27H, 3 x $\text{Si}(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ_{C} 141.5 (C-21), 132.8 (C-18), 131.6 (C-19), 124.1 (C-20), 86.8, 80.9, 79.7, 76.8, 74.8, 67.7, 55.2, 41.4, 37.0, 26.1, 26.0, 26.0, 23.8, 22.6, 18.5, 18.5, 18.3, 14.9, 14.3, 12.0, 7.2, 6.8, 0.7, -3.6, -3.8, -3.9, -4.3, -5.3, -5.4; HRMS (ES+) calc. for $\text{C}_{45}\text{H}_{97}\text{IO}_6\text{Si}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 1023.5068, found 1023.5069.

(6*S*,7*S*,8*R*,9*E*,11*E*,13*R*,14*R*,15*R*,16*R*,18*Z*,20*S*,21*S*,22*R*,23*S*,25*R*,28*R*)-14,15,23-tris((*tert*-Butyldimethylsilyl)oxy)-31,31-diethyl-13-methoxy-21-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,12,16,20,24,25,28-dodecamethyl-6,28-bis((triethylsilyl)oxy)-7-((trimethylsilyl)oxy)-4,30-dioxo-3,31-disilatrtriaconta-9,11,18-triene (360)



A solution of iodide **370** (20.0 mg, 0.021 mmol, 1.25 equiv.) in Et₂O (0.3 mL) was stirred over crushed CaH₂ for 30 min. After cooling to –78 °C, *t*-BuLi (1.7 M in pentane, 74 μL, 0.127 mmol, 7.5 equiv.) was then added and the reaction mixture stirred for 3 min. OMe-9-BBN (1 M in hexanes, 0.21 mL, 0.212 mmol, 12.5 equiv.) was then added, followed by THF (0.3 mL). The reaction mixture was then stirred for 5 min at –78 °C before being warmed to rt and stirred for 1 h. Pd(dppf)Cl₂ (1.7 mg, 16.8 μmol, 0.1 equiv.), K₃PO₄ (3 M aq, 17 μL, 0.050 mmol, 3.0 equiv.), vinyl iodide **196** (14.7 mg, 0.017 mmol, 1.0 equiv.) and degassed DMF (0.3 mL) were then added. The reaction mixture was then stirred for 3 h and quenched with H₂O (1 mL). The layers were separated and the organic layer extracted with Et₂O (4 x 1 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40:1 PE/Et₂O) to give the title compound as a pale-yellow oil (15.1 mg, 54%).

R_f 0.69 (9:1 PE/EtOAc); [α]_D²⁰ + 7.5 (*c* 0.72, CHCl₃); **IR** (thin film, ν_{max} /cm⁻¹): 3459, 2952, 2343, 1520, 1445, 1370, 1097, 834; **¹H NMR** (500 MHz, CDCl₃): δ _H 7.25 (2H, d, *J* = 8.5 Hz, H-Ar), 6.86 (2H, d, *J* = 8.5 Hz, H-Ar), 6.19 (1H, dd, *J* = 15.0, 10.8 Hz, H-20), 5.95 (1H, d, *J* = 10.8 Hz, H-19), 5.68 (1H, dd, *J* = 15.0, 7.9 Hz, H-21), 5.55 (1H, t, *J* = 10.5 Hz, H-11), 5.30 (1H, dt, *J* = 10.5, 7.1 Hz, H-12), 4.56 (1H, d, *J* = 10.9 Hz, OCH₂Ar), 4.43 (1H, d, *J* = 10.9 Hz, OCH₂Ar), 4.13 (1H, br d, *J* = 9.8 Hz, H-7), 3.80 (3H, s, ArOCH₃), 3.74 (1H, d, *J* = 8.3 Hz, H-17), 3.63 (1H, d, *J* = 9.8 Hz, H-25a), 3.61 (1H, d, *J* = 8.0 Hz, H-15), 3.57 (1H, d, *J* = 8.3 Hz, H-16), 3.50 (1H, d, *J* = 1.50 Hz, H-23), 3.42 (1H, d, *J* = 9.8 Hz, H-25b), 3.39 (1H, d, *J* = 9.5 Hz, H-1a), 3.31 (1H, d, *J* = 9.5 Hz, H-1b), 3.12-3.08 (4H, m, H-9, OCH₃), 2.76 (1H, dqd, *J* = 7.9, 7.1, 1.5 Hz, H-22), 2.71-2.65 (1H, m, H-10), 2.46 (1H, dd, *J* = 13.5, 7.1 Hz, H-13a), 1.96-1.90 (1H, m, H-8), 1.84-1.79 (1H, m, H-13b), 1.65 (3H, s, Me-18), 1.50-1.20 (8H, m, H-3, H-4, H-5, H-6, H-14), 1.16 (3H, s, Me-24), 1.15 (3H, s, Me-2), 1.04-0.80

(78H, Me-5, Me-8, Me-10, Me-14, Me-22, 4 x Si(CH₃)₃), 3 x Si(CH₂CH₃)₃), 0.63-0.55 (18H, m, 3 x Si(CH₂-CH₃)₃), 0.12-0.01 (33H, 4 x Si(CH₃)₂, Si(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃): δ_c 158.7 (C-Ar), 141.2 (C-21), 135.2 (C-11), 132.9 (C-18), 131.6 (C-19), 131.3 (C-Ar), 128.4 (C-Ar), 127.6 (C-12), 124.2 (C-20), 113.6 (C-Ar), 86.6 (C-15), 84.6 (C-9), 80.9 (C-23), 79.7 (C-16), 76.8 (C-25), 75.9 (C-17), 74.0 (C-Bn), 69.9 (C-1), 69.5 (C-7), 67.7 (C-24), 65.9 (C-2), 55.3 (OMe), 55.2 (OMe), 42.9, 41.4, 38.8, 37.3, 37.0, 36.4, 36.0, 33.9, 33.7, 32.0, 31.3, 29.0, 27.7, 26.2, 26.0, 25.9, 25.3, 23.8, 22.6, 20.4, 19.4, 18.8, 18.5, 18.1, 14.3, 11.9, 11.4, 10.3, 7.2, 6.8, 4.4, 0.7, -3.7, -3.8, -4.1, -4.1, -4.6, -4.6, -5.3, -5.4; HRMS (ES+) calc. for C₈₇H₁₇₈O₁₁Si₈N [M+NH₄]⁺ 1642.1884, found 1642.1881.

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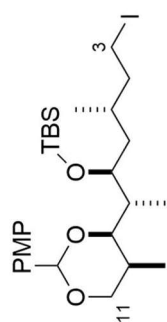
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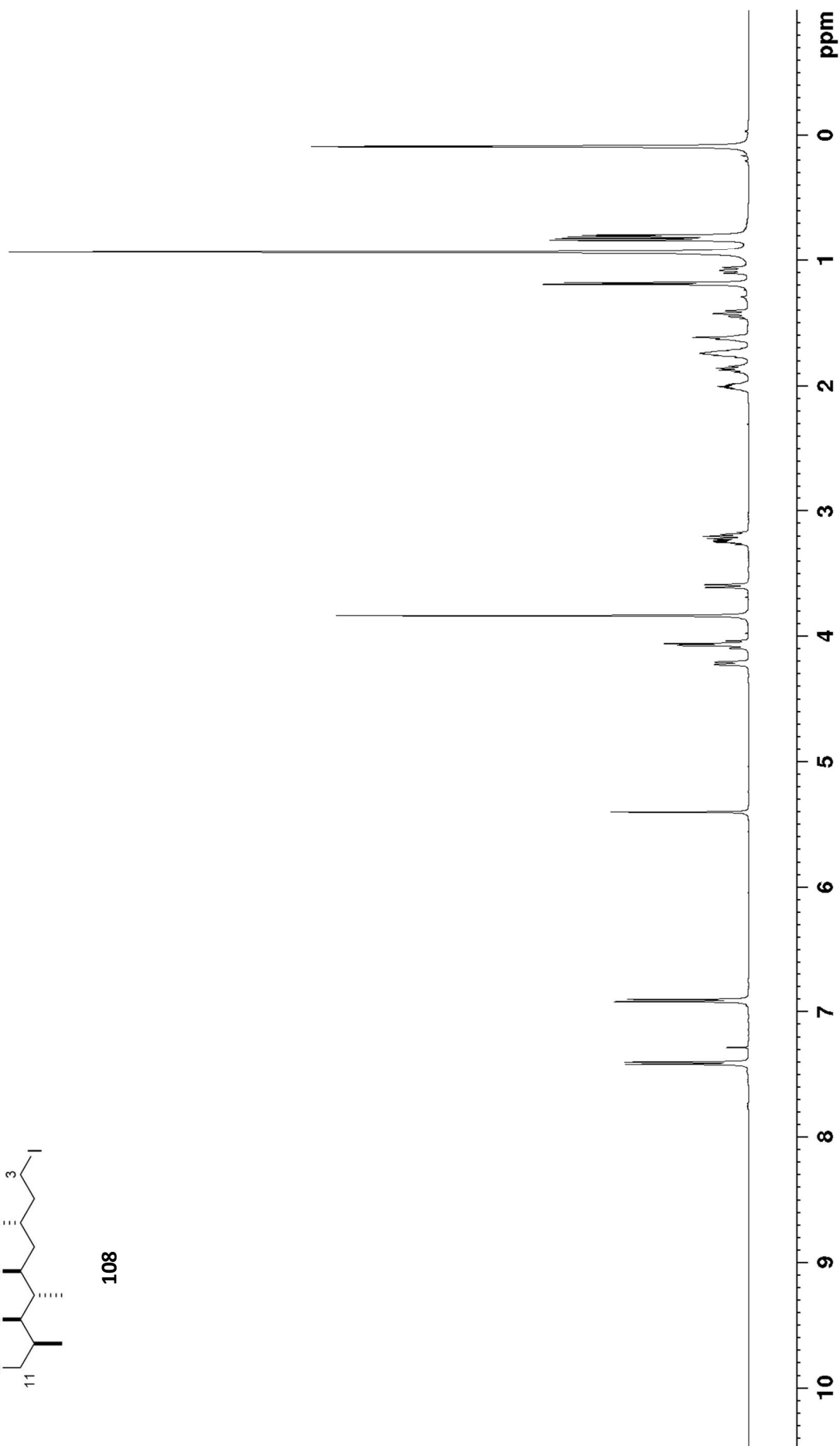
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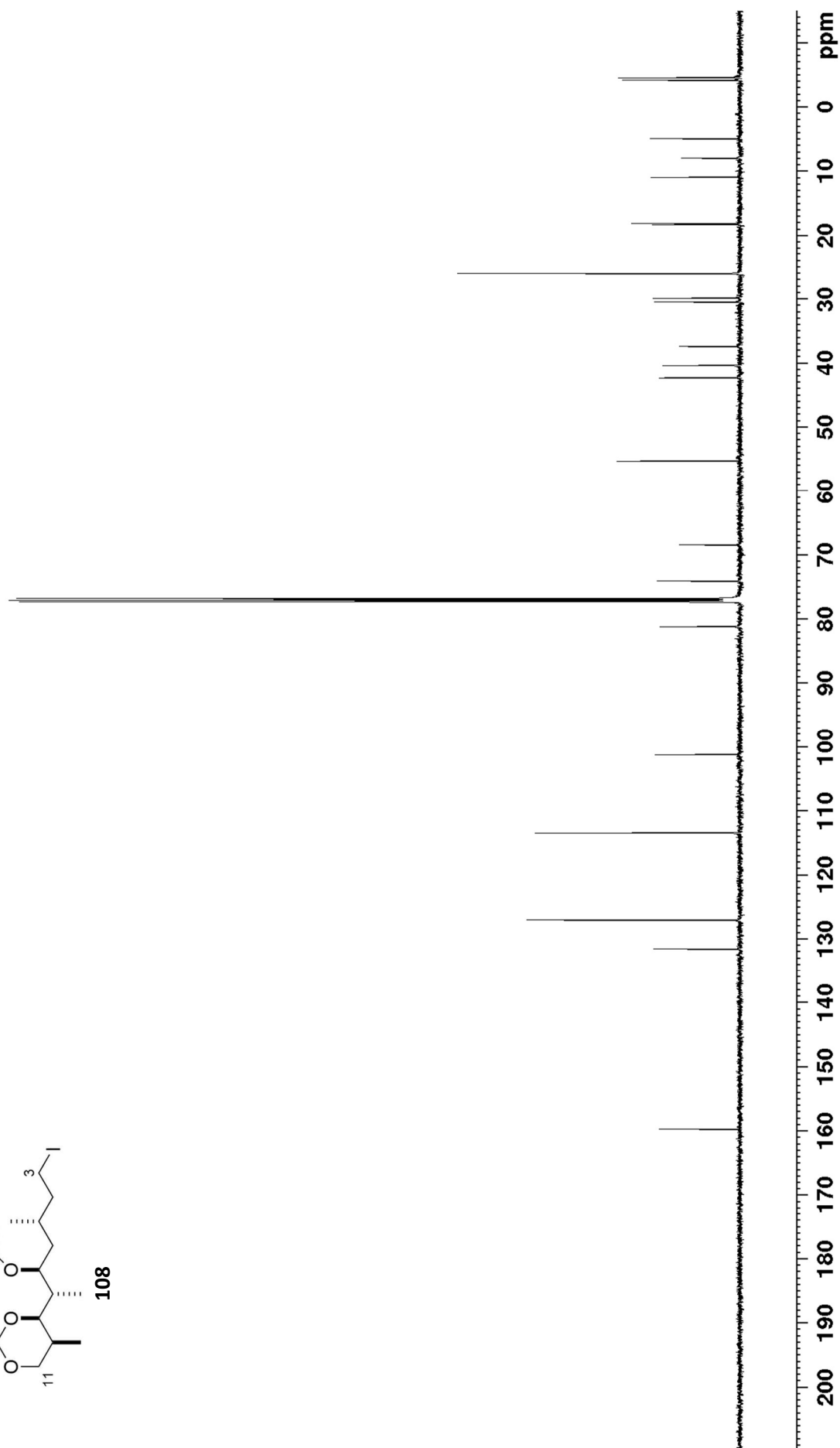
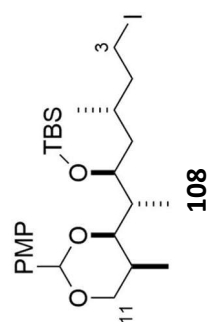
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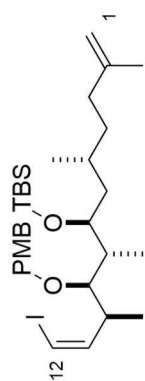
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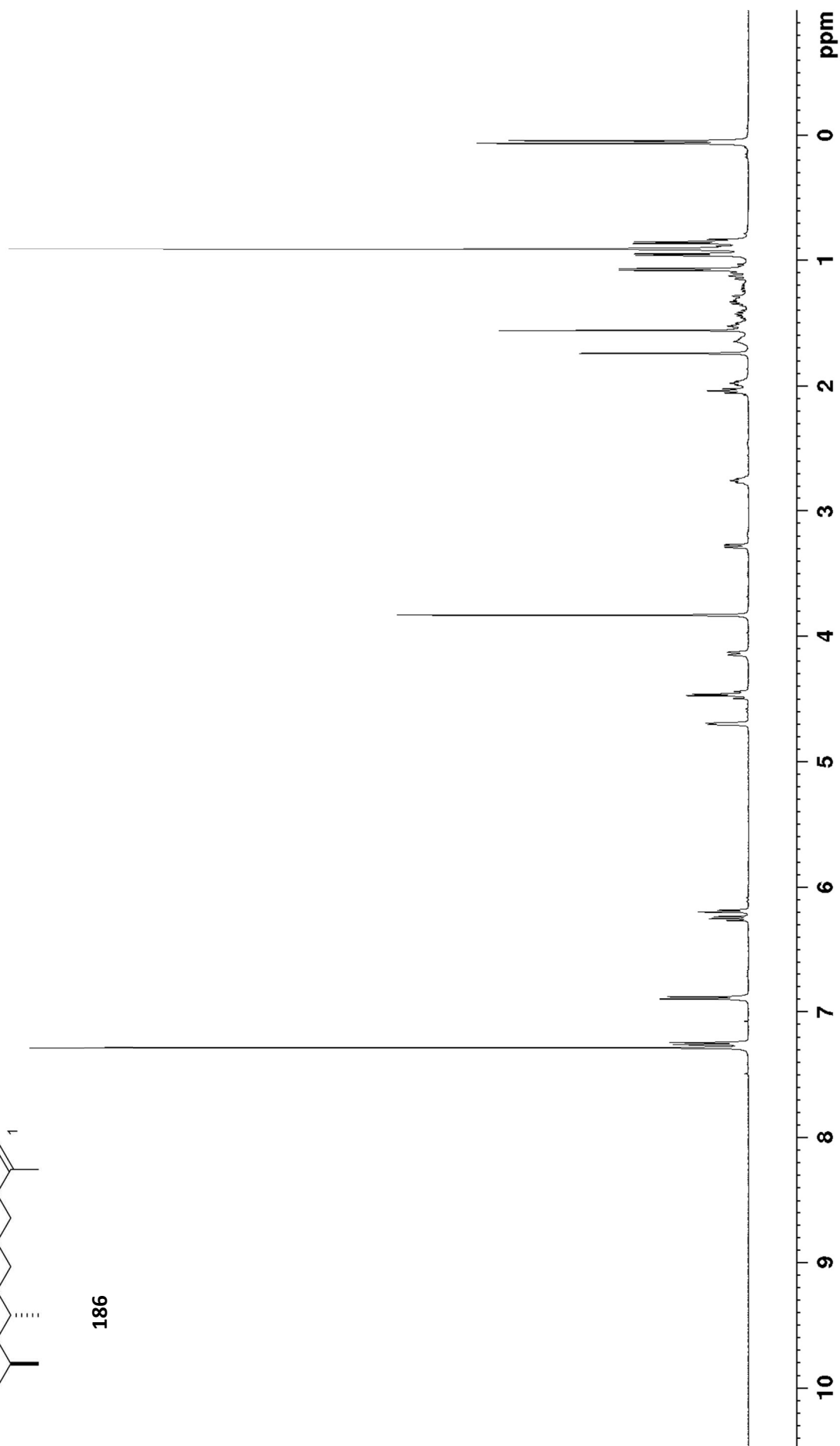
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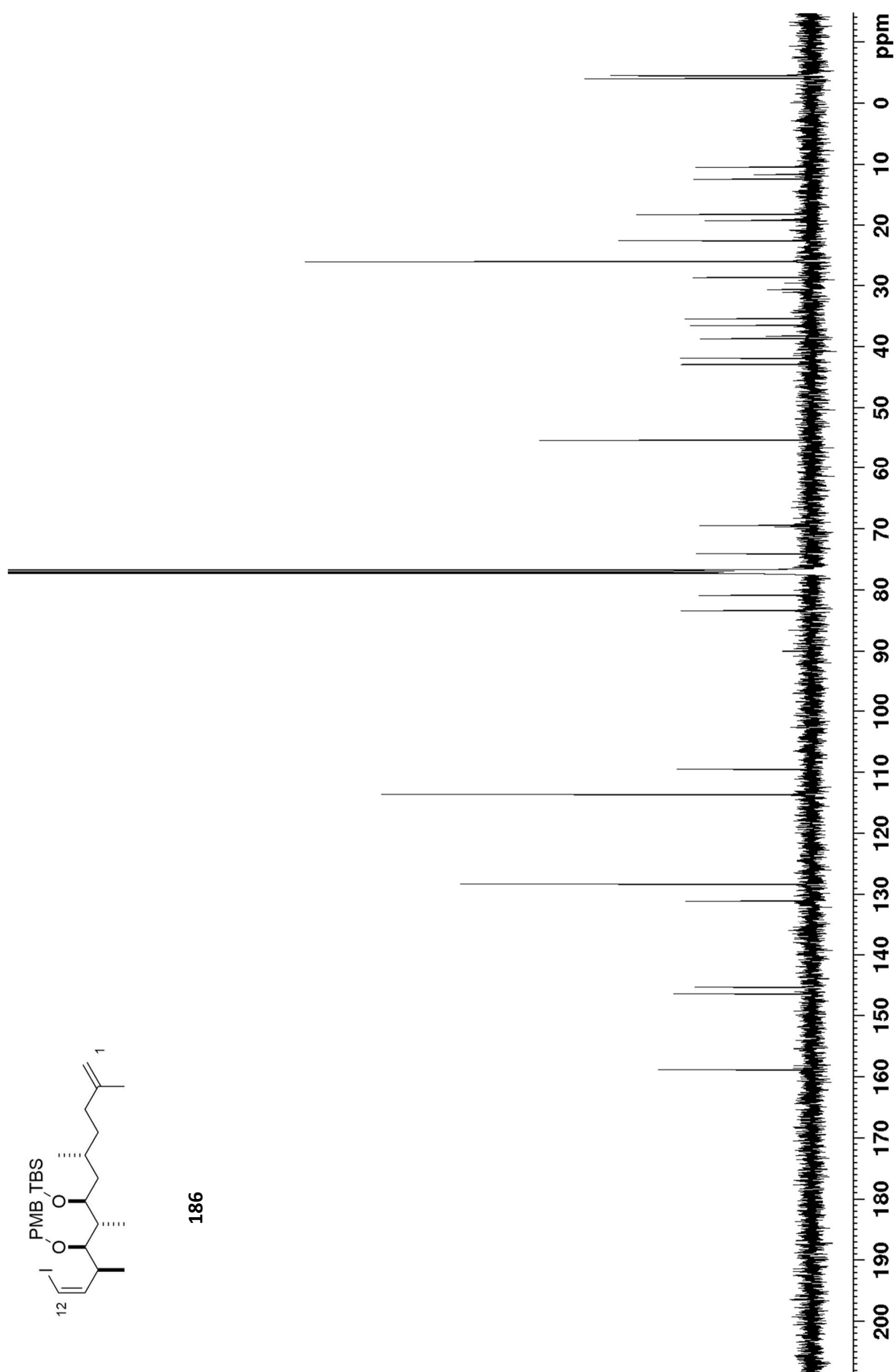


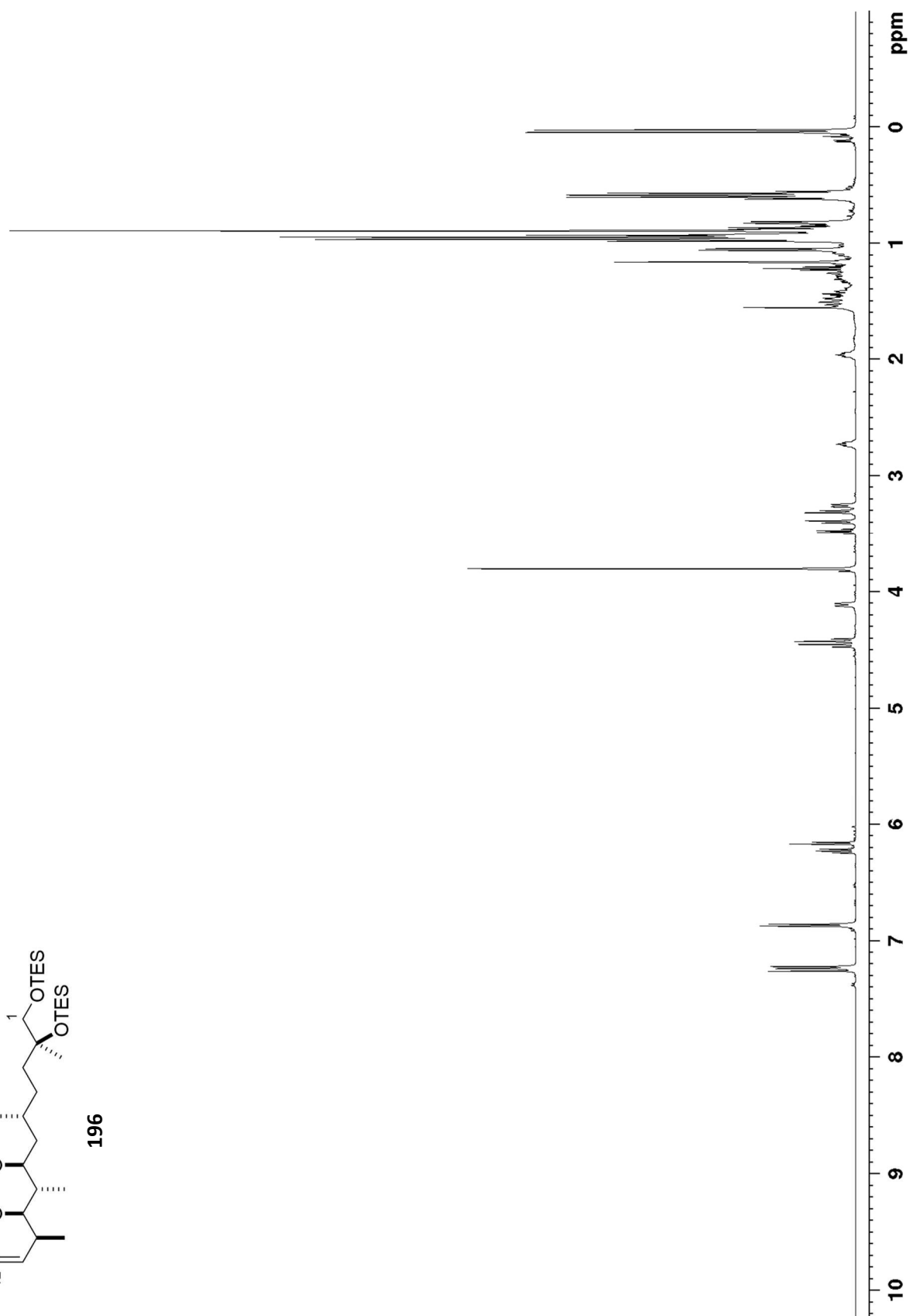


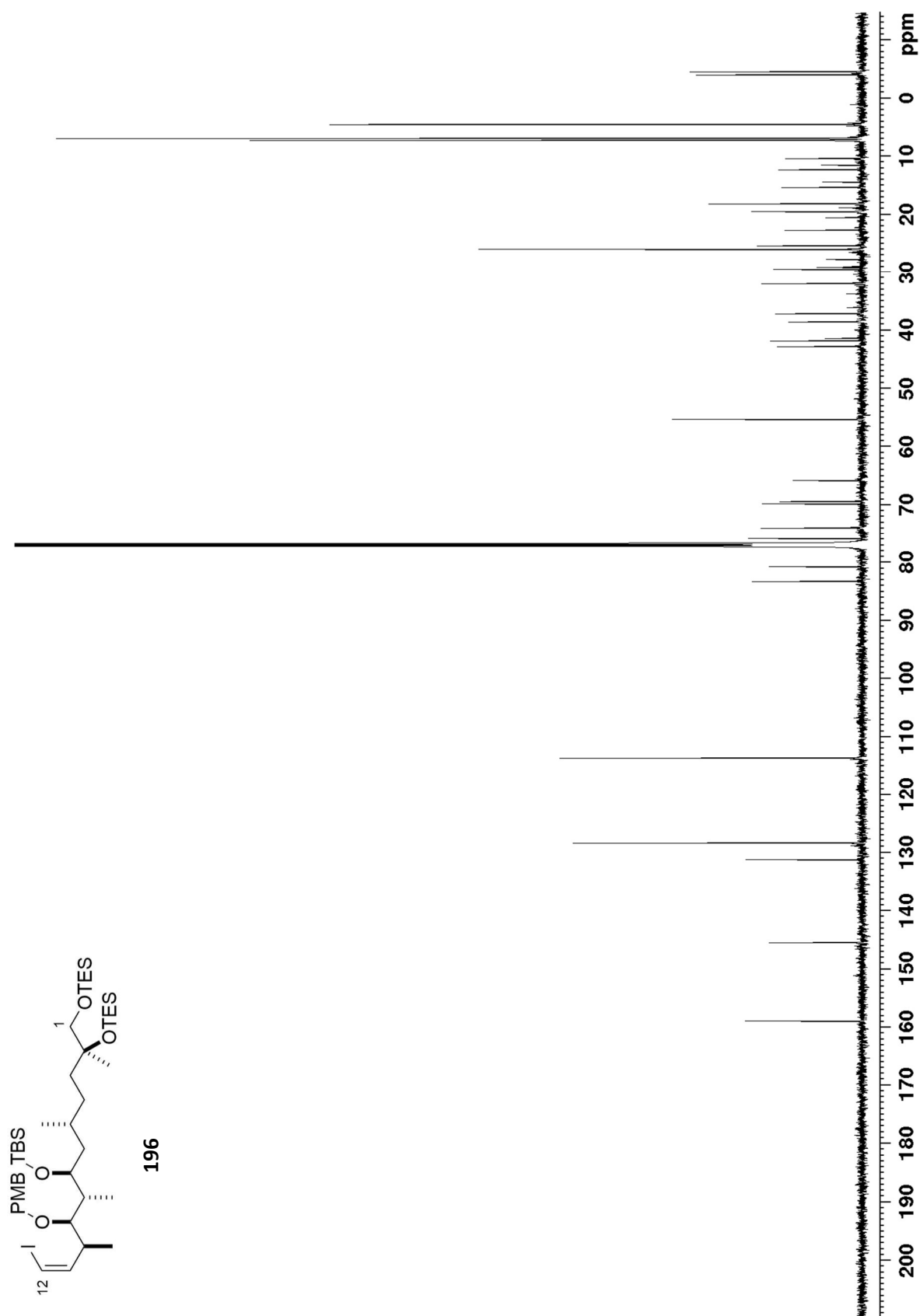


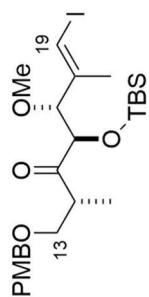
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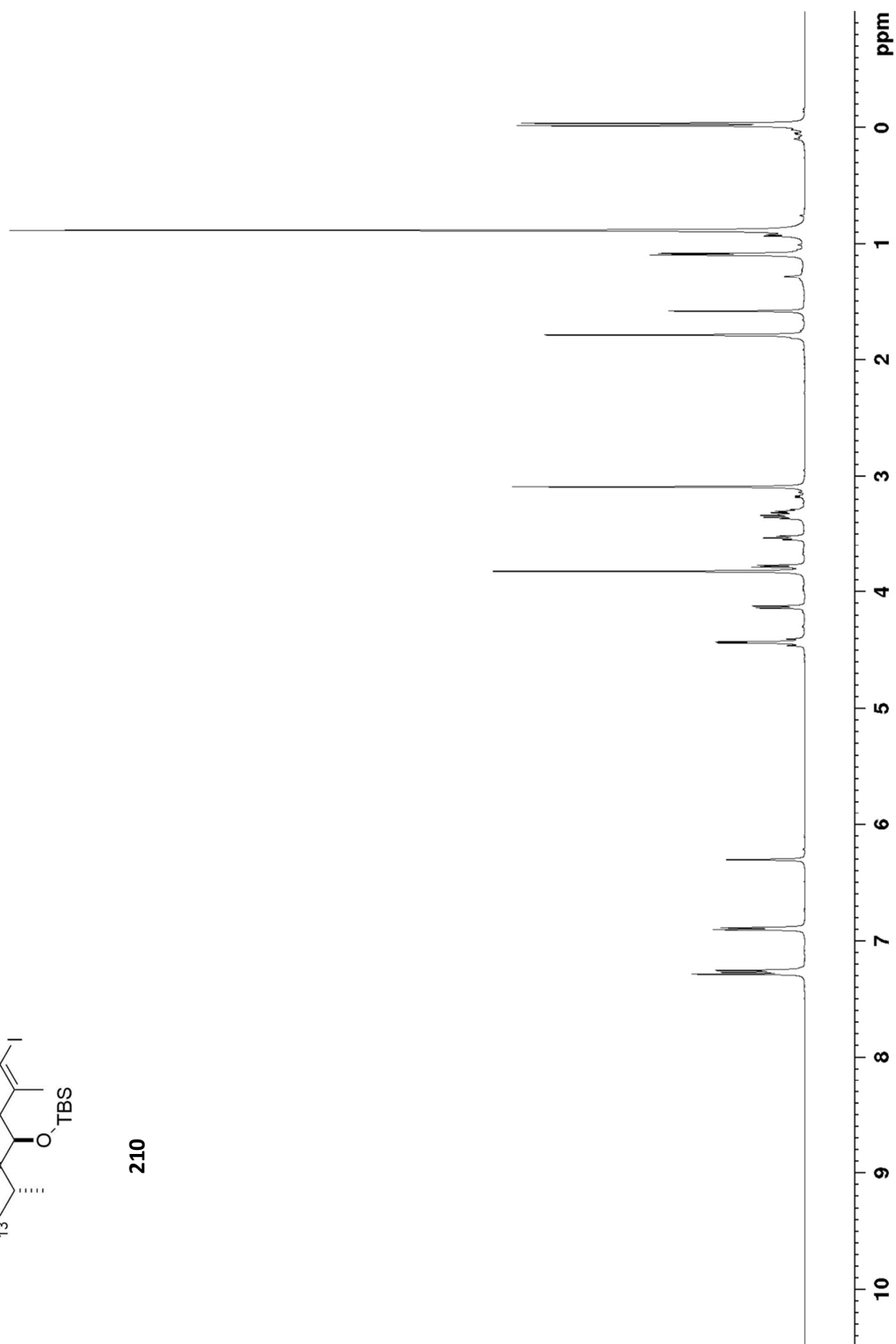


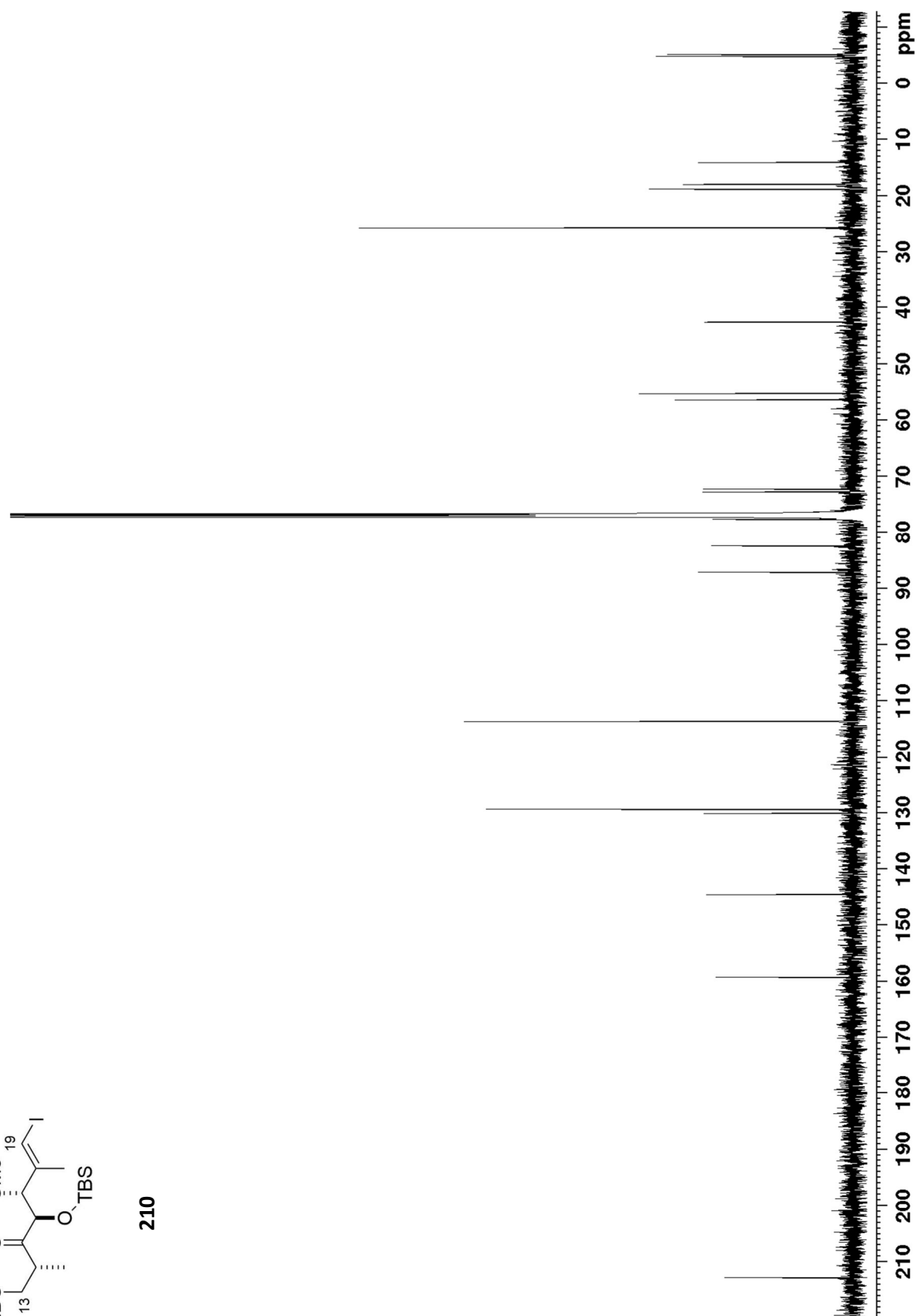


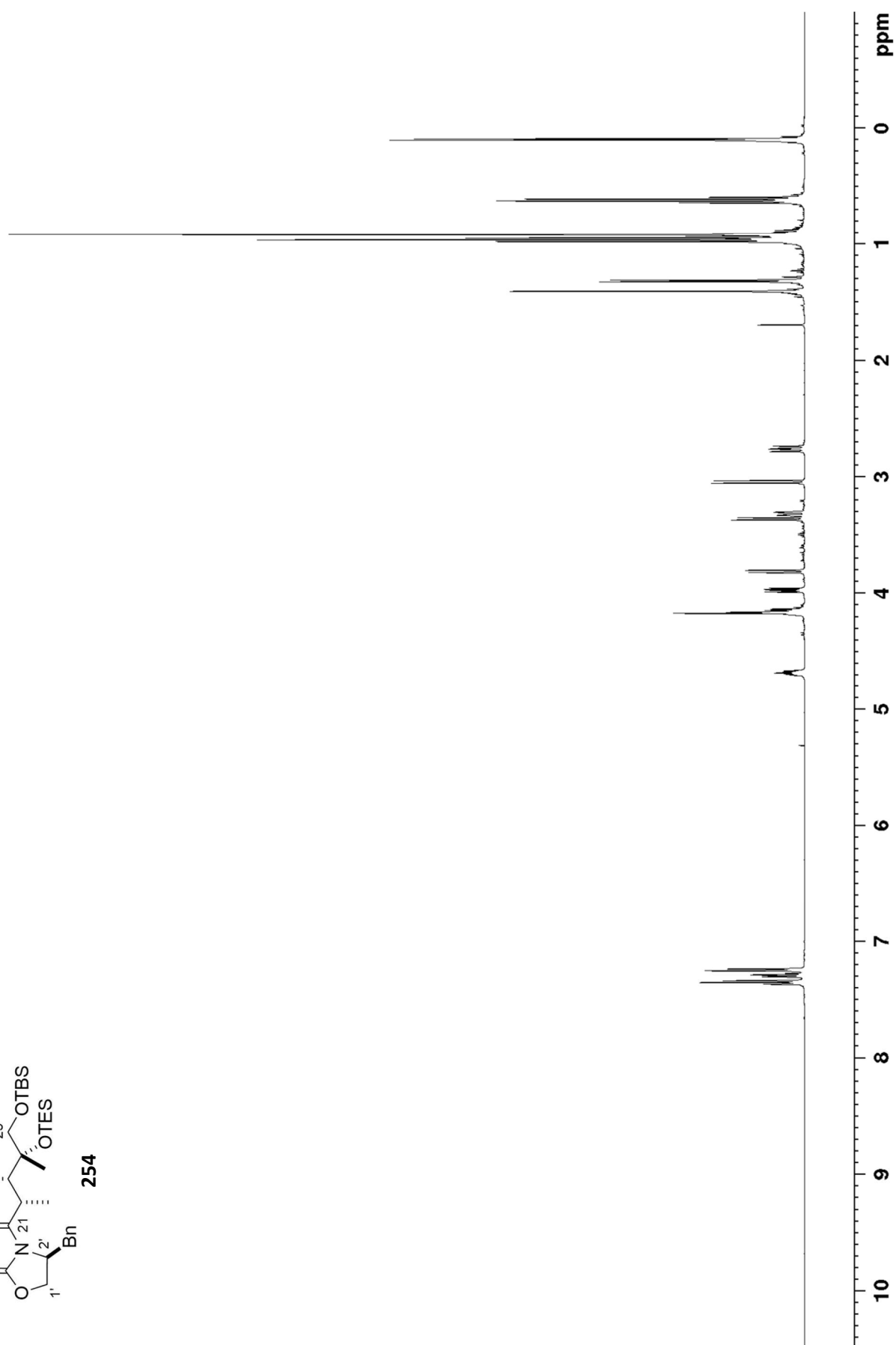
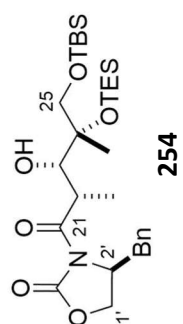


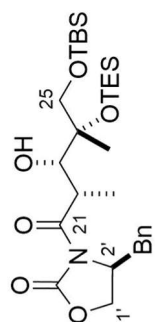


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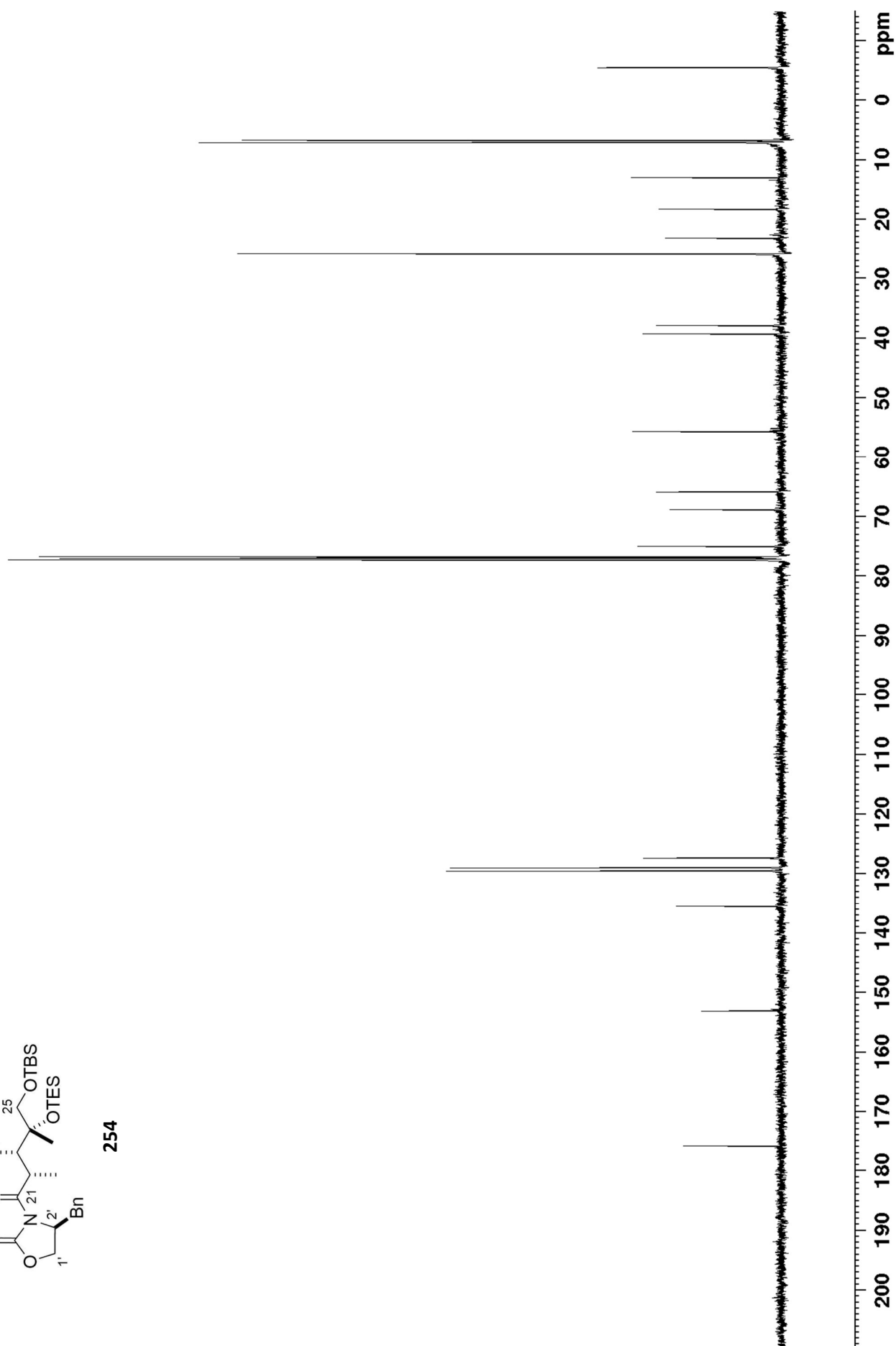


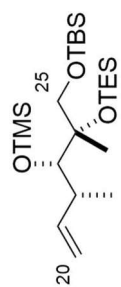
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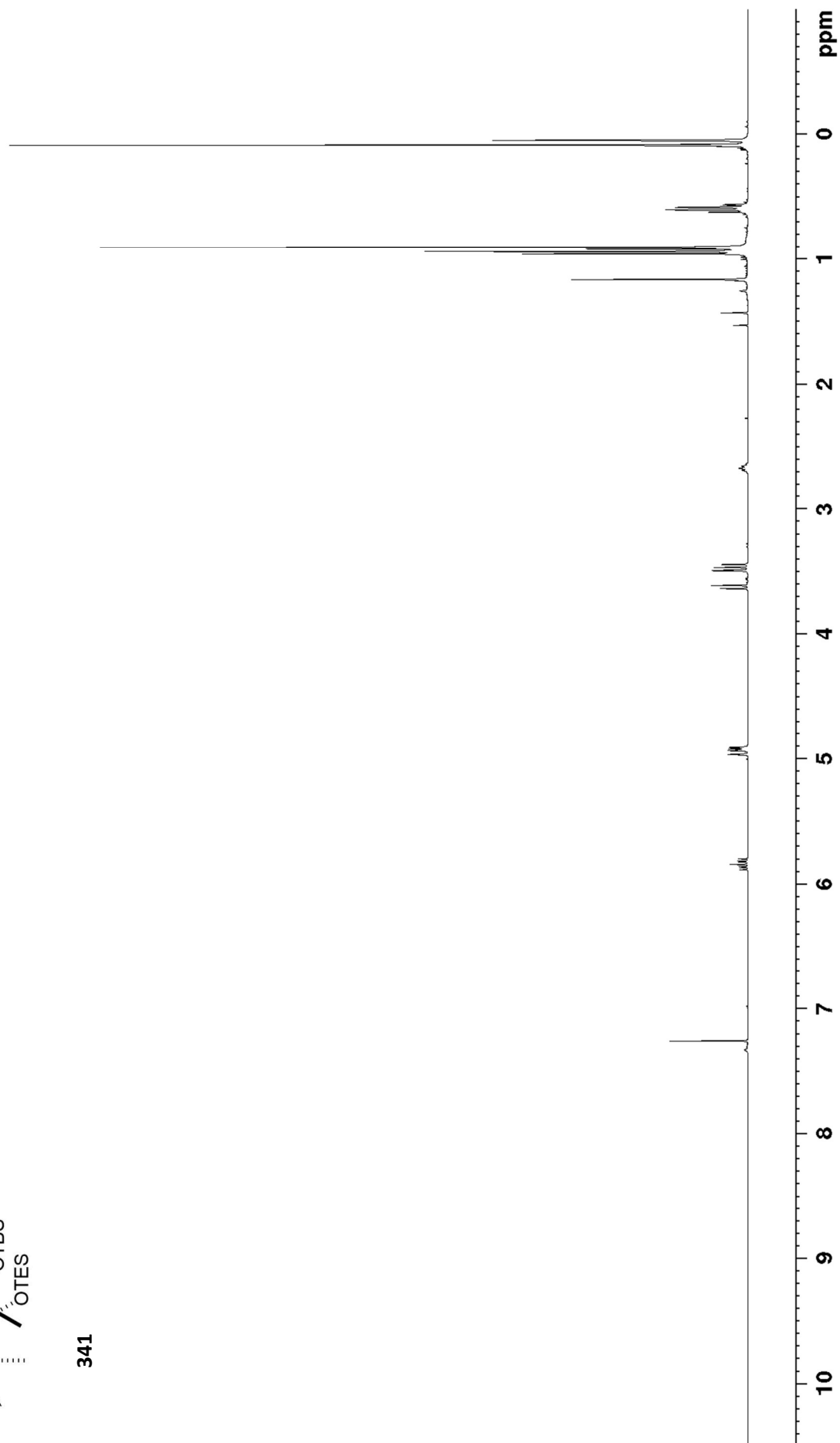


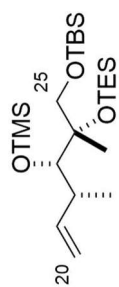
254



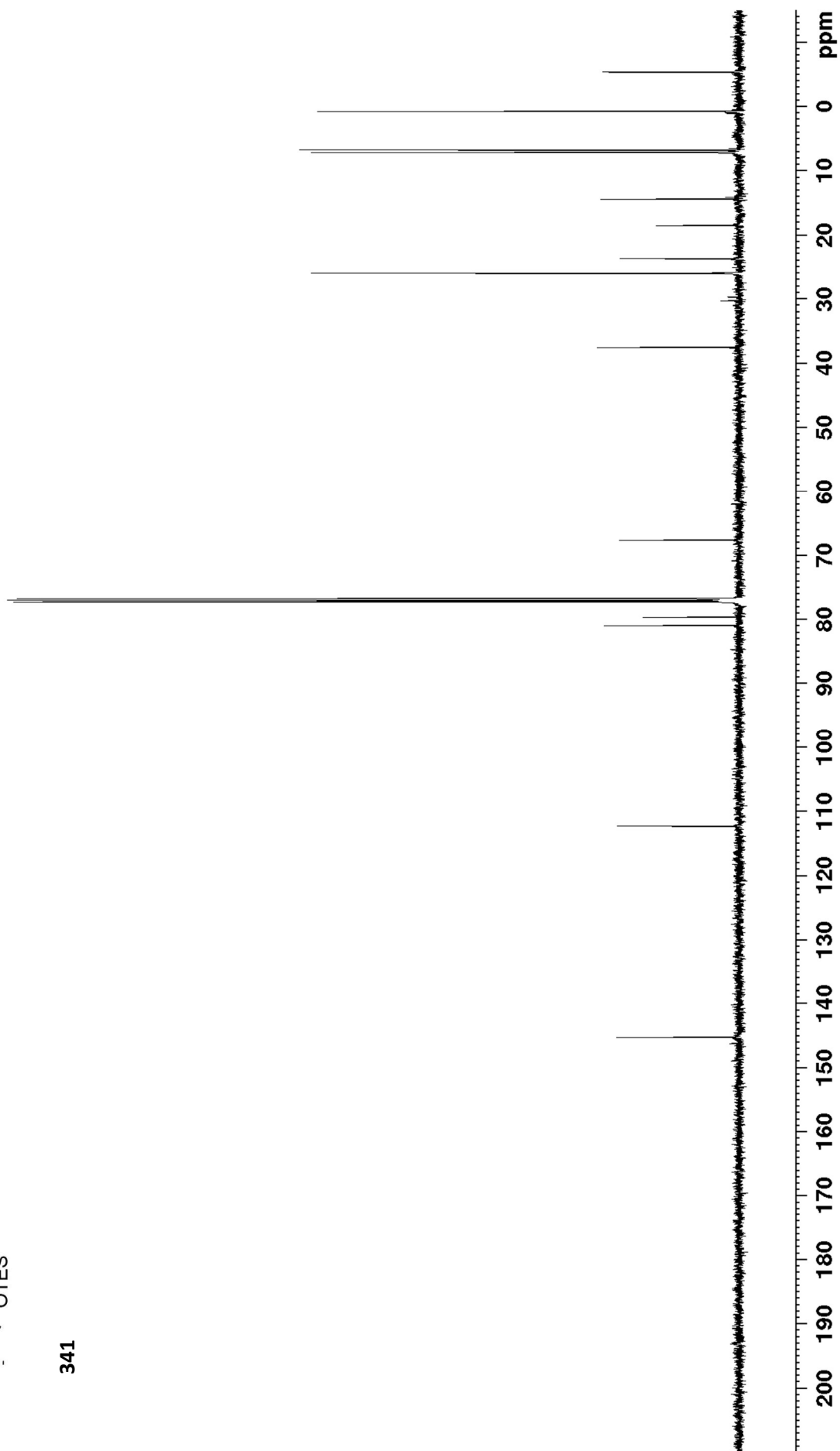


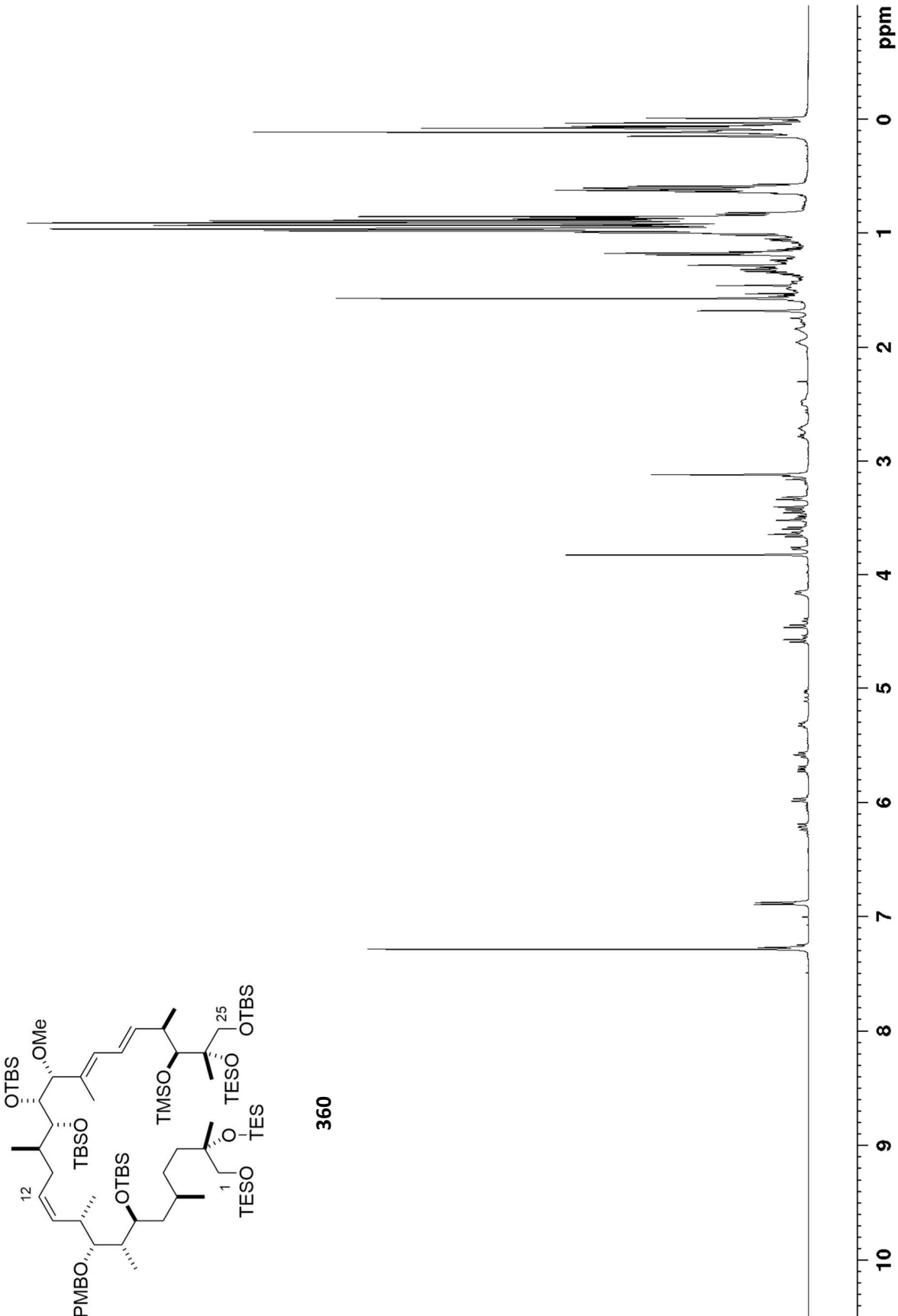
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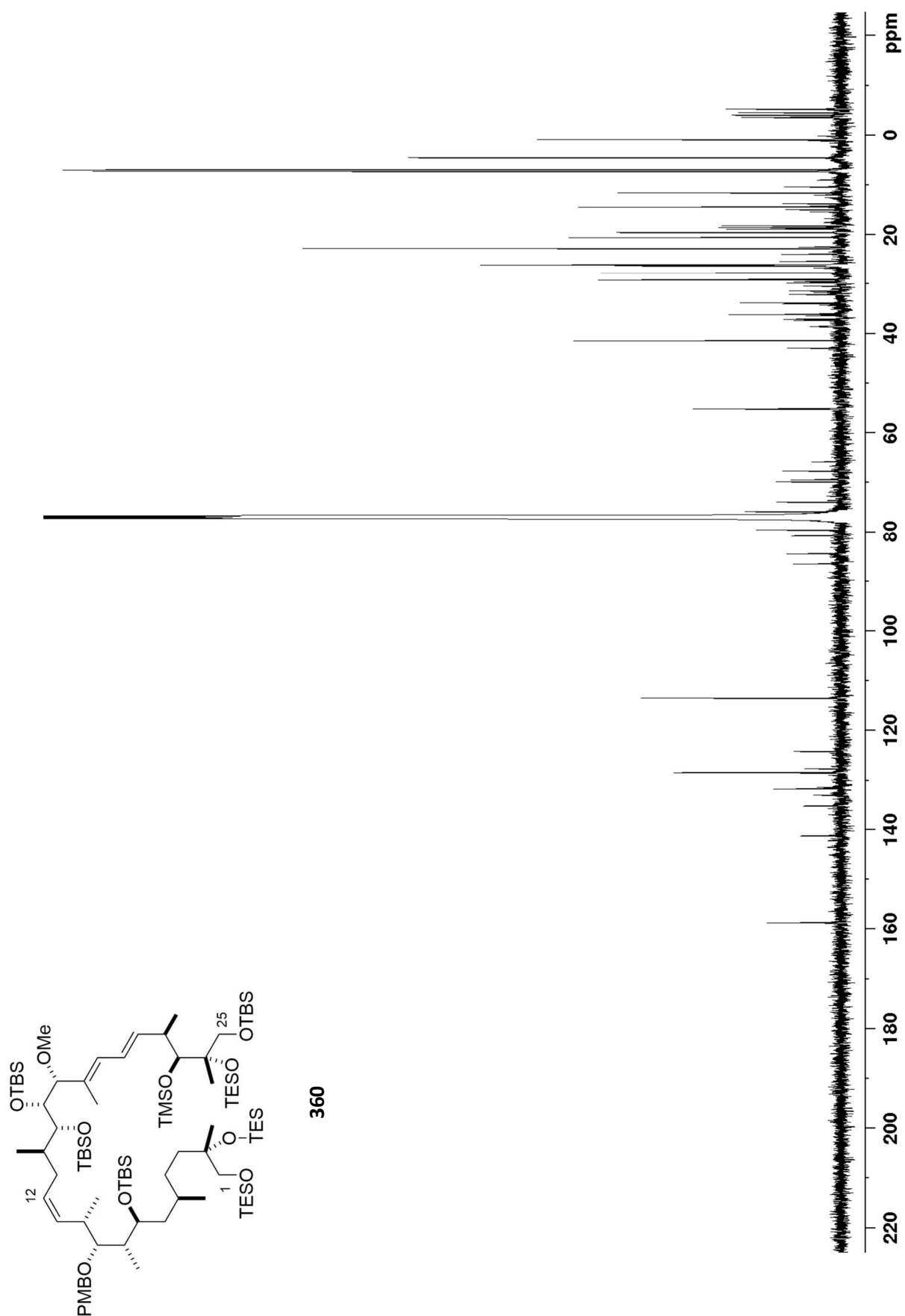




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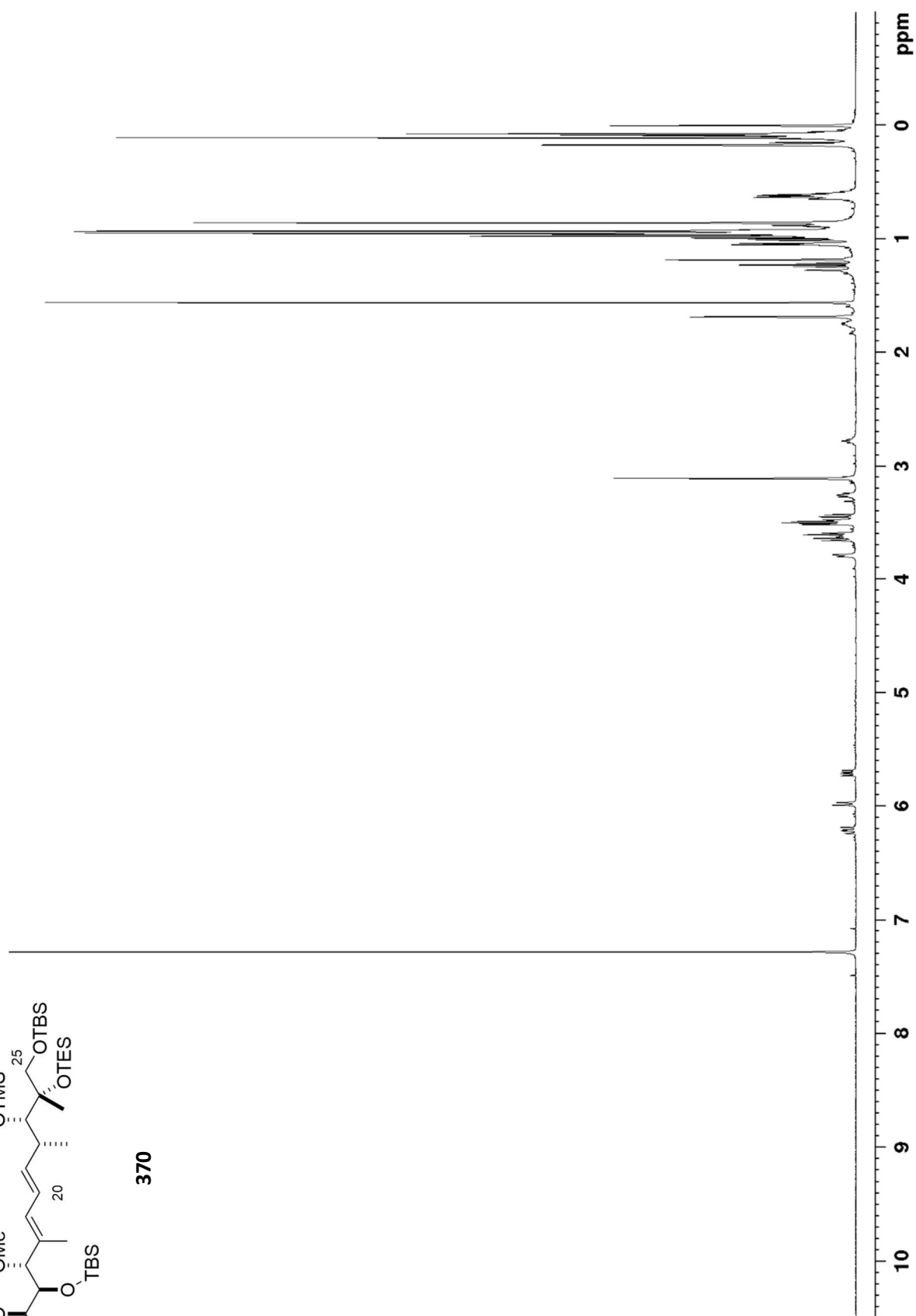


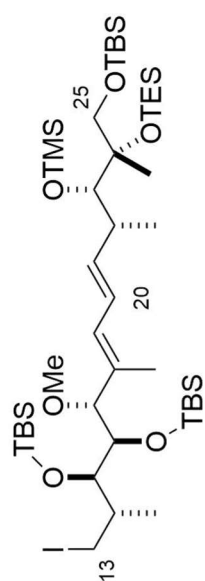




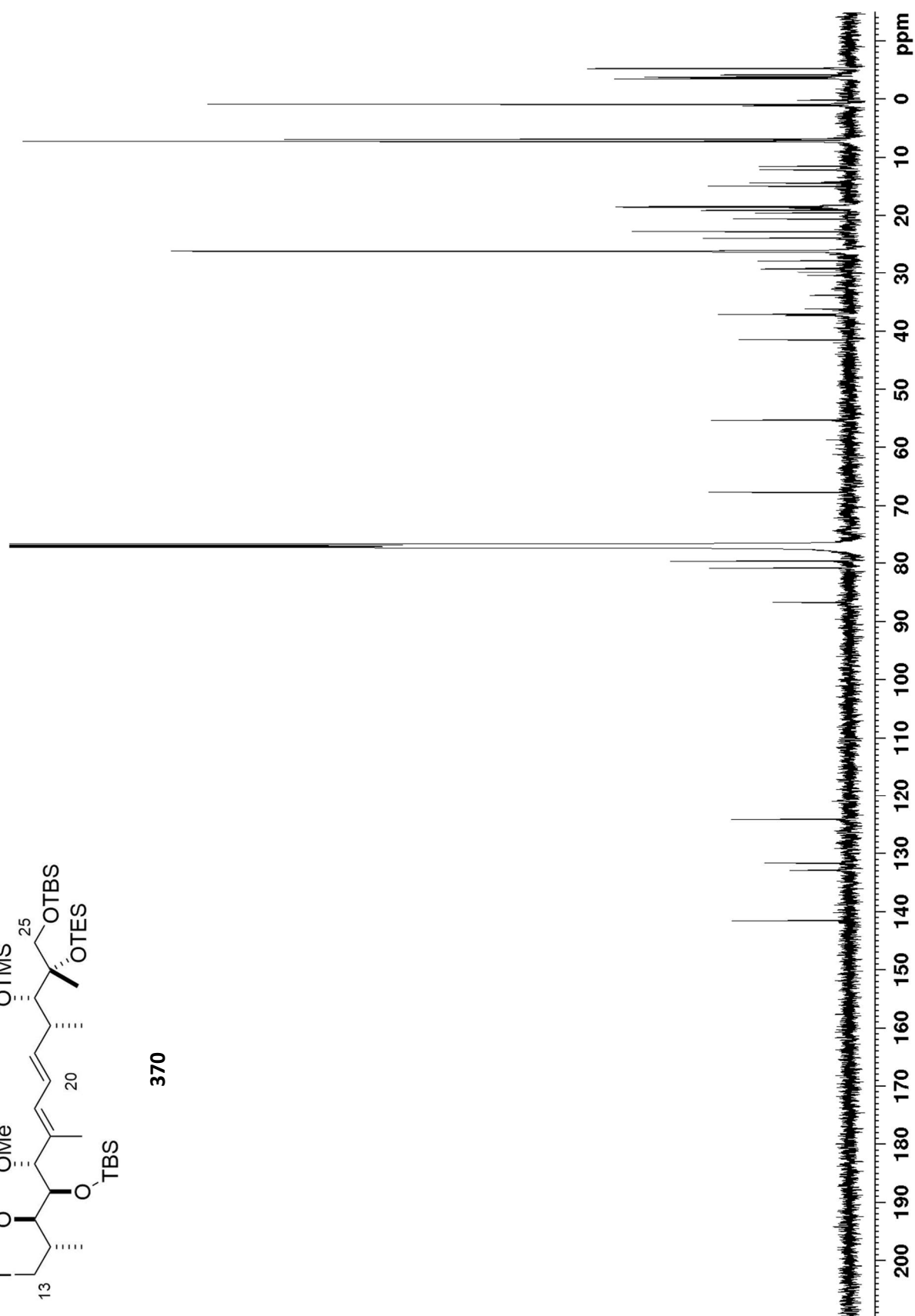
360

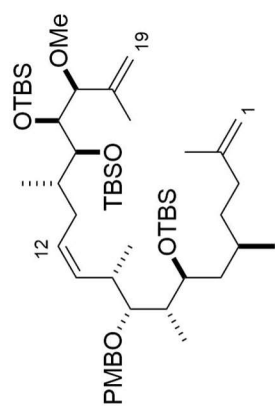
Chemical structure of compound 10, a branched polyene. The molecule features a central chain with a double bond between carbons 20 and 25. Substituents include a TBS group on the left, an OTMS group on the right, and a TBS group on the bottom branch. The structure is labeled with carbons 13, 20, and 25.



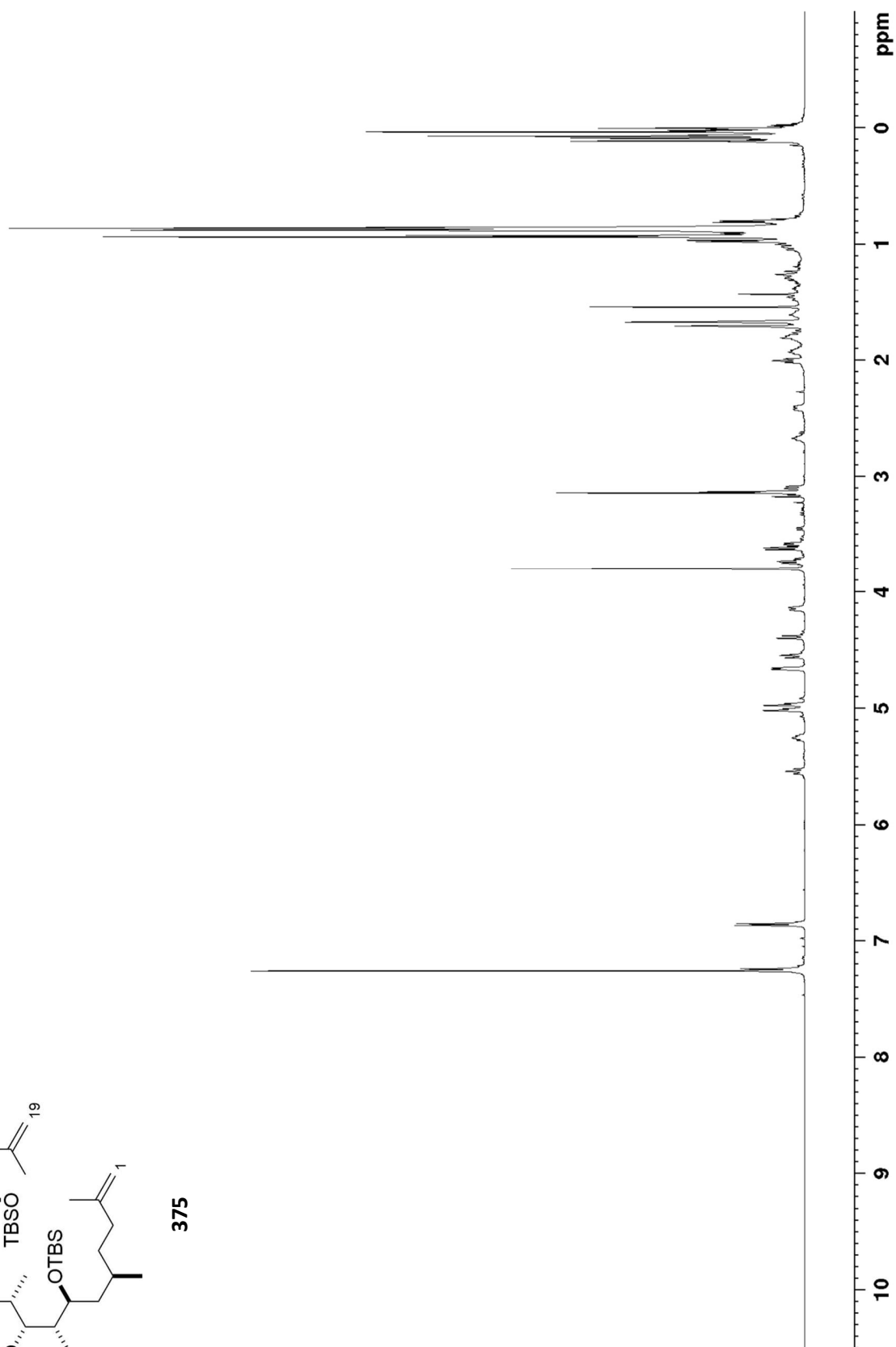


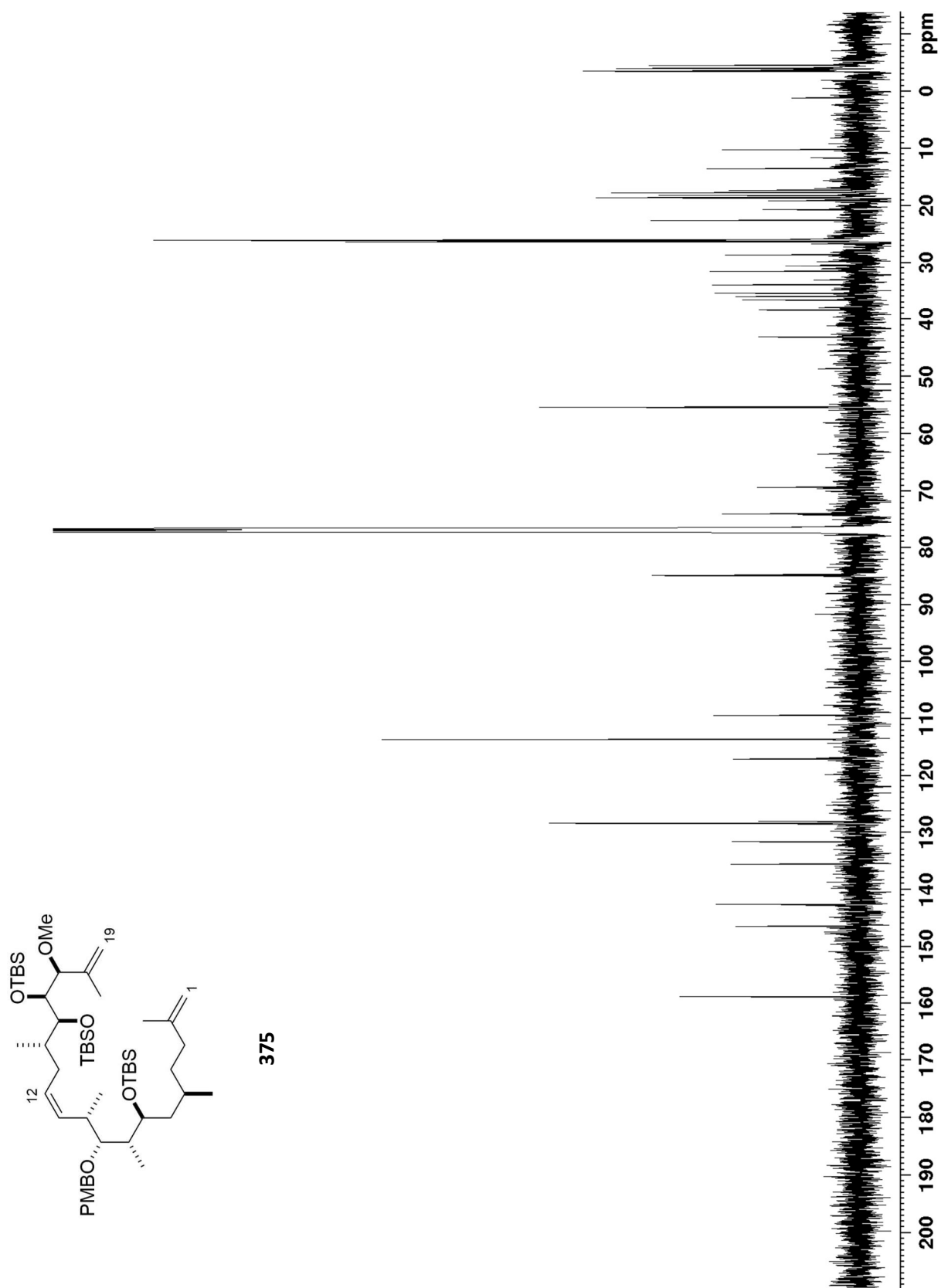
370



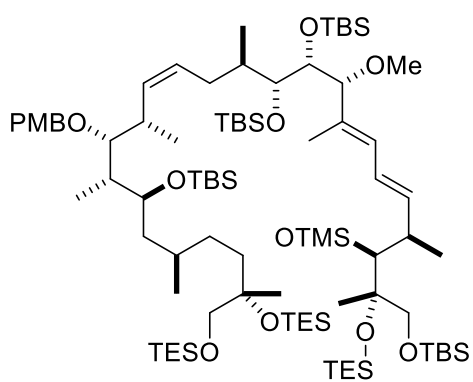


375

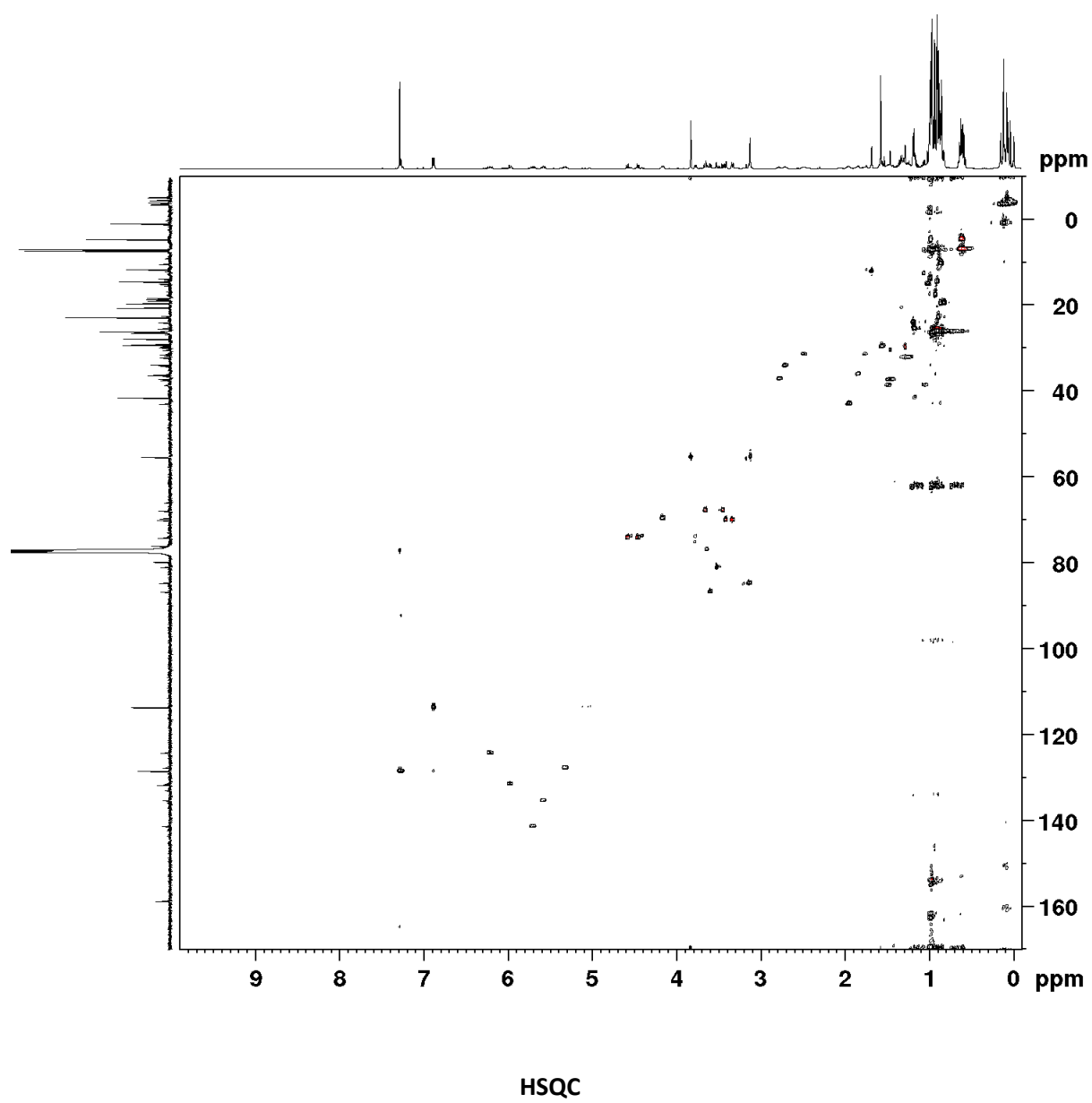


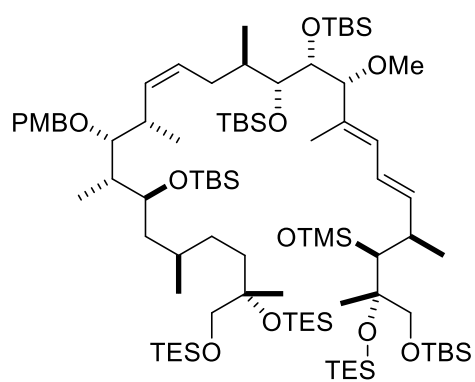


375

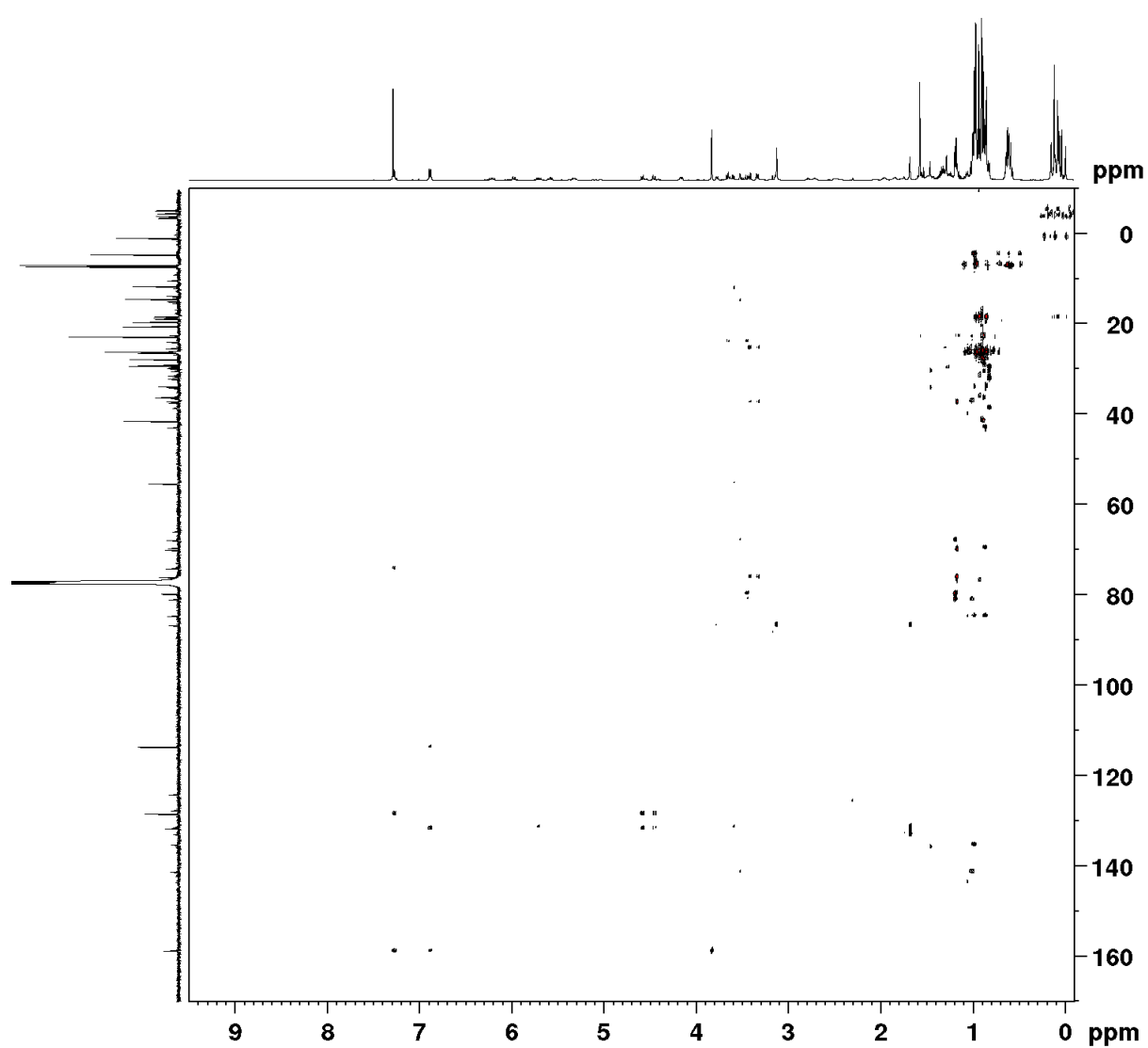


360





360



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